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A Second Synthesis of *D*-Apio-*β*-*D*-furanosyl Maleimide as a Structural Analogue of Showdomycin

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Summary. Apioshowdomycin (3-(*D*-apio-*β*-*D*-furanosyl)-1*H*-pyrrole-2,5-dione, **2**) has been prepared as an analogue of the C-nucleoside showdomycin (**1**) in seven steps, starting from 2,3-O-isopropylidene-*D*-apio-*D*-furanose (**8**). The key step is the addition of a radical generated from apiosyl bromide **5b** to (*E*)-methyl 3-cyanoacrylate (**4**).

Keywords. Showdomycin; Apioshowdomycin; C-Nucleoside; *Tris*(trimethylsilyl)silane; 2,3-O-Isopropylidene-*D*-apio-*D*-furanose.

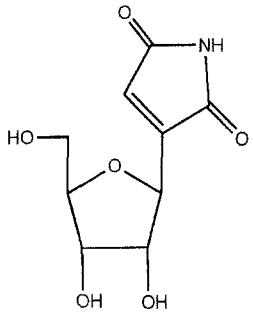
Eine zweite Synthese von *D*-Apio-*β*-*D*-furanosylmaleimid als Strukturanaloges von Showdomycin

Zusammenfassung. Apioshowdomycin (3-(*D*-apio-*β*-*D*-furanosyl)-1*H*-pyrrol-2,5-dion, **2**) wurde als Analoges des C-Nucleosids Showdomycin (**1**), ausgehend von 2,3-O-Isopropyliden-*D*-apio-*D*-furanose (**8**), in sieben Stufen hergestellt. Der Schlüsselschritt ist die Addition eines aus dem Apiosylbromid **5b** generierten Radikals an (*E*)-Methyl-3-cyanoacrylat (**4**).

Introduction

D-(+)-Showdomycin (**1**) is one of the members of the small C-nucleoside family and has been isolated from culture filtrates of *Streptomyces showdoensis* [1]. Because of its antitumor and antibacterial activity, it has attracted much interest resulting in a fairly large number of syntheses of this natural product [2]. Showdomycin consists of a ribose and a maleimide subunit joined together by a C–C bond. In a recently published paper [3], we have reported on the synthesis of apioshowdomycin (3-(*D*-apio-*β*-*D*-furanosyl)-1*H*-pyrrole-2,5-dione, **2**), differing from showdomycin with respect to the position of the ribofuranose ring to which the hydroxymethyl side chain is attached. The basic sugars are *β*-*D*-ribofuranose and *D*-apio-*β*-*D*-furanose, respectively.

Our first synthesis of apioshowdomycin was based on the generation and manipulation of an apiosyl nitrile to introduce the crucial C–C bond [3]. The synthesis disclosed here relies on a radical based C–C bond formation which is feasable *via* addition of an apiosyl radical to an activated olefin. We have



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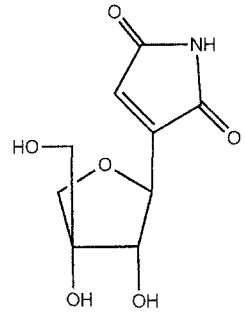

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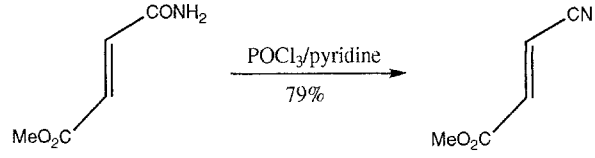
Fig. 1. Structures of showdomycin and apioshowdomycin

successfully used this approach to the synthesis of a variety of C-piosides [4]. (*E*)-Methyl 3-cyanoacrylate was selected as advanced precursor for the maleimide part of the molecule. Cyclization of the cyano ester was assumed to afford a substituted succinimide amenable to introduction of the C–C double bond. The last part of the synthesis is related to the synthesis of racemic showdomycin as reported by *Kozikowski* and *Ames* [5] who used a totally different approach to obtain the cyano ester in the ribose series which was further manipulated to showdomycin.

Results and Discussion

The first building block, the required (*E*)-methyl 3-cyanoacrylate **4**, was prepared in 79% yield by dehydration [6] of amide **3** [7] which is available in three steps from maleic anhydride *via* fumaric acid monomethyl ester and the corresponding acid chloride [8] by literature procedures (Scheme 1).

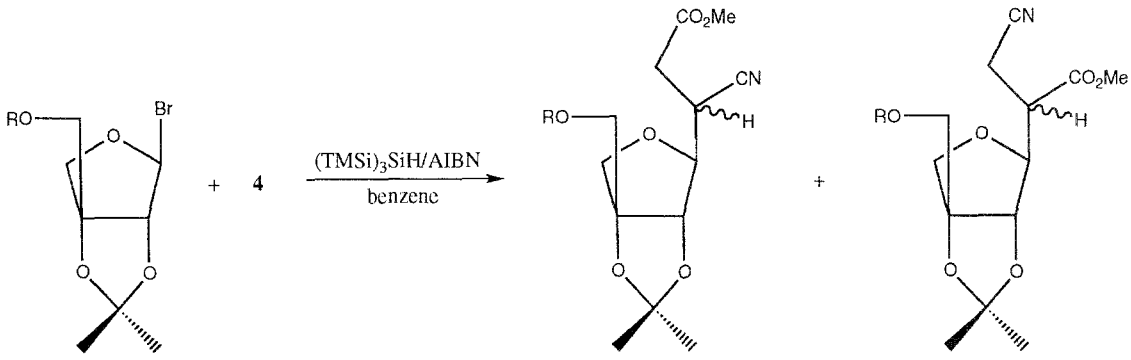


3 4

Scheme 1

The second building block was the protected apiosyl bromide **5a** [4]. The benzoate group, although of limited stability under basic conditions, was selected because compounds **5a** can be prepared easily in two steps from 2,3-O-isopropylidene-*D*-apio-*D*-furanose. The coupling of the two subunits was effected by dropwise addition of *tris*(trimethylsilyl)silane to a refluxing benzene solution of **5a** (R = Bz), excess cyano acrylate **4**, and *AIBN* under argon (Scheme 2) [4].

Four diastereomers were formed caused by the regioselectivity of the radical addition and the generation of a new chiral centre. Two spots corresponding to reaction products were detected by TLC (hexane/ethyl acetate, 4:1, R_f = 0.30 and 0.24). Flash chromatography yielded fractions **6a** (R_f = 0.30) and **7a** (R_f = 0.24) in a ratio of 1:5 in a combined yield of 84%. The assignment of structures of **6a** and



5a,b

a: R = Bz
b: R = TBDPS

6a,b + 7a,b

6a + 7a: 84%
6b + 7b: 93%

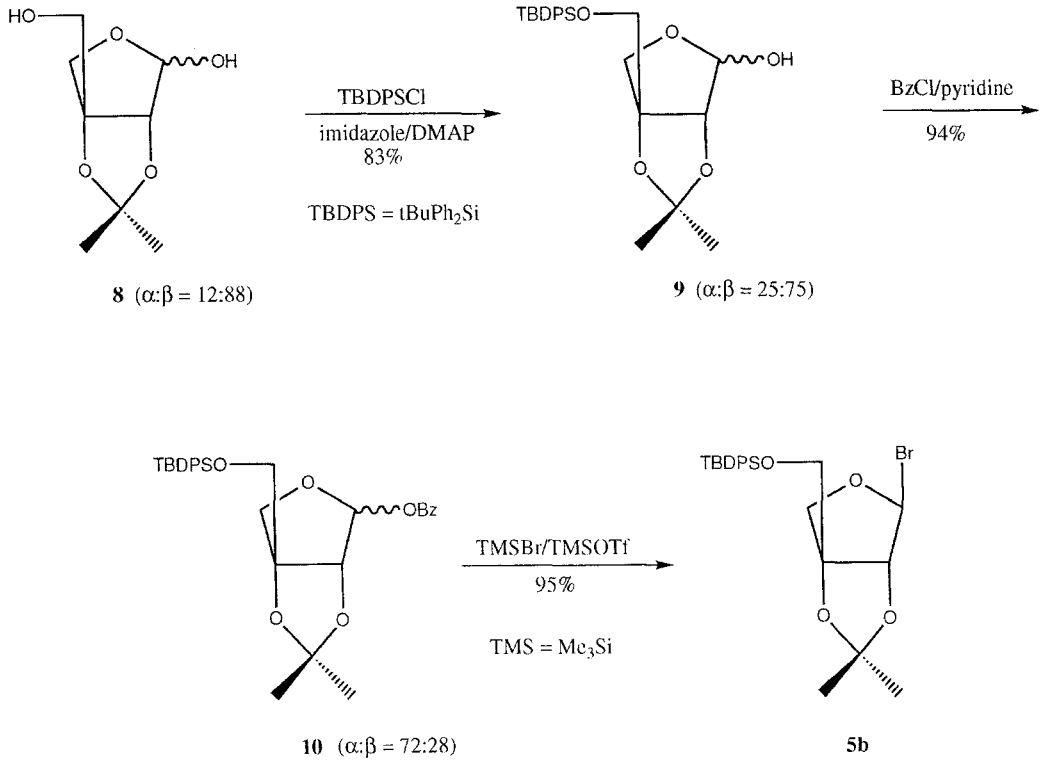
Scheme 2

7a is based on the ^{13}C chemical shifts of the CH_2 and CH groups having either CO_2Me or CN as substituents. Data obtained by searching a ^{13}C NMR data base reveal that carbon atoms attached to a CN group resonate at higher field than those attached to a CO_2Me moiety with the other substituents being comparable. Fraction **6a** consists of one compound as shown by ^1H NMR spectroscopy. The ^{13}C NMR spectrum exhibits diagnostic signals at 33.54 (CH_2CO_2Me) and at 29.15 (*C*HCN) ppm. Fraction **7a** is a mixture of three diastereomers (A : B : C = 50 : 33 : 17) with diagnostic ^{13}C NMR signals for CH_2CN (16.97 (**A**), 17.26 (**B**)), $CHCO_2Me$ (43.10 (**A**), 44.06 (**B**)), and for **C** (31.12 (*C*HCN), 33.51 (CH_2CO_2Me) ppm). The configurations at the newly formed asymmetric centres C-1′ remain open. The main reaction products **A** and **B** are therefore formed by the addition of the apiosyl radical *β* to the cyano group. The *β* configuration at the anomeric centres is deduced by analogy to the reactions of radicals generated from apiosyl bromide **5a** and the methylthio(thiocarbonyl) derivative of 5-O-benzoyl-2,3-O-isopropylidene-*D*-ribofuranose [4, 9]. The small coupling constants ($J_{1,2}$ = 2.0 Hz (**6a**), 2.0 Hz (**A**), 3.0 Hz (**B**), and 3.5 Hz (**C**) are in agreement with a *β*-configuration for all four diastereomers formed. The pairs of compounds **A** and **B** and **C** and **6a** differ by the configuration at C-1′ and whether CN or CO_2Me is bound to C-1′. It is not necessary for the further manipulation to separate the cyano esters as they will eventually lead to the same product (**2**).

The cyclization of the mixture of all four cyano esters was tried under a variety of conditions such as different temperatures and concentrations of MeONa in methanol. The benzoate group was removed prior or after cyclization, and mixtures of succinimides diastereomeric at C-1′ and having both *α*- and *β*-configuration were formed. Under these too basic conditions, the tetrahydrofuran ring was opened by *β*-elimination and formed again to afford both *α*- and *β*-configurated apiosyl succinimides. Cyclization with $Na_2CO_3/H_2O_2(30\%)/H_2O$/acetone was also not a clean reaction [5]. Two mixtures of main products having *β*-configuration were isolated in low yields. One of them contained the desired succinimides with the benzoate group intact; the other one consisted of the amide esters without the

benzoate protecting group. These failures, in part attributed to the base labile benzoate group, forced us to abandon this approach to **2** *via* **6a/7a**.

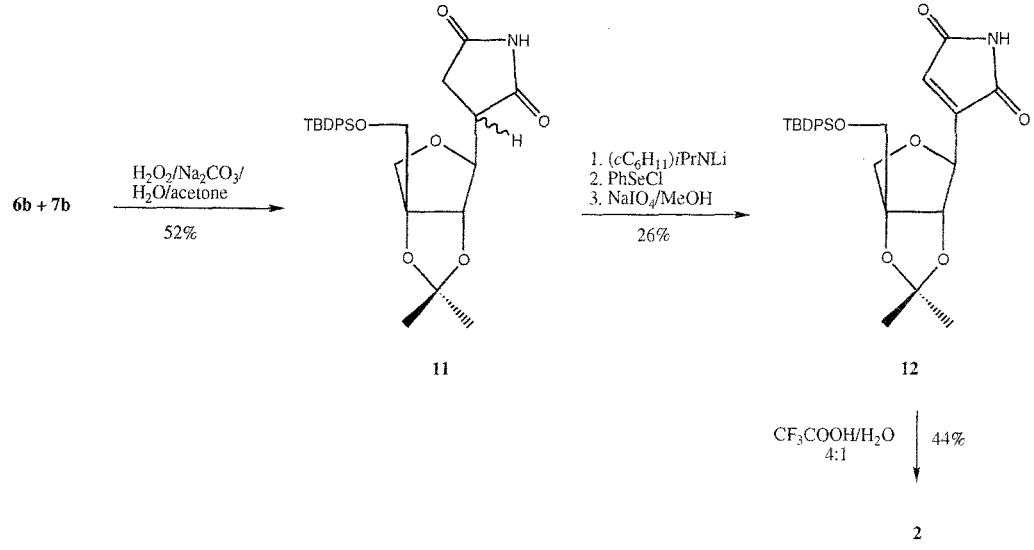
The apiosyl bromide **5b** with $R = {}^{t}BuPh_2Si$ (*TBDPS*) as protecting group, being more stable towards bases and acids than the benzoate group, was tested next as radical precursor. 2,3-O-Isopropylidene-*D*-apio-*D*-furanose (**8**; $\alpha : \beta = 12 : 88$) [10] was silylated with *TBDPS*Cl (1.2 equiv.)/imidazole/*DMAP* to give mainly (83%) monosilylated product **9** beside a small amount (16%) of disilylated one (Scheme 3). The chromatographically homogenous compound **9** was an anomeric mixture ($\alpha : \beta = 25:75; \alpha : J_{1,2} = 3.0$ Hz, $\beta : J_{1,2} = 0$ Hz). When the pure β-anomer of **8** was silylated with a stoichiometric amount of *TBDPS*Cl and the reaction mixture was allowed to warm up from $-20°C$ instead of 0°C to room temperature, only monosilylated product **9** with $\alpha : \beta = 8 : 92$ was isolated in 74% yield. Esterification of **9** with benzoyl chloride/pyridine afforded benzoate **10** ($\alpha:\beta = 72:28; \alpha:J_{1,2} = 4.0$ Hz, $\beta:J_{1,2} = 0$ Hz) which was transformed into apiosyl bromide **5b** in 95% yield. The purity of the crude product as checked by ^1H NMR spectroscopy was high, and only the β-anomer ($J_{1,2} = 0$ Hz) was present. It was not chromatographed because it hydrolyzed on silica. As both anomers of benzoate **10** are cleanly transformed into β-bromide **5b**, it is not necessary to start with the pure β-anomer of **8**.



Scheme 3

The bromide was used immediately to generate a radical which adds smoothly to (*E*)-methyl 3-cyanoacrylate (**4**) to produce again four diastereomers in 93% combined yield (Scheme 2) [4]. The mixture could be separated as before into

fractions **6b** and **7b** (ratio 1:6 to 1:8), having R_f values in hexane/ethyl acetate (10:1) of 0.30 and 0.25, respectively. Fraction **6b** is nearly homogenous as judged by spectroscopy and results from the addition of the radical β to the ester function of the activated olefin **4** (^{1}H NMR: $J_{1,2} = 1.0$ Hz; ^{13}C NMR: $\delta = 33.62$ (CH_2CO_2Me) and about 28.47 (*C*HCN) ppm). Fraction **7b** is again a mixture of three diastereomers in a similar ratio as before (**A**:**B**:**C** = 49 : 35 : 16). The major components **A** and **B** result from the addition of the radical β to the cyano function of the activated olefin **4** (^{1}H NMR: 2.5 Hz (**A**), $J_{1,2} = 1.5$ Hz (**B**); ^{13}C NMR: $\delta = 16.92$ (**A**) and 16.83 (**B**) for CH_2CN, 43.73 (**A**) and 42.63 (**B**) ppm for $CHCO_2Me$). The minor component **C** (^{1}H NMR: $J_{1,2} = 3.0$ Hz; ^{13}C NMR: $\delta = 30.97$ (*C*HCN), 33.57 (CH_2CO_2Me) ppm) corresponds to component **C** of fraction **7a**. The C–C bond formation between apiosyl bromides **5a** and **5b** and (*E*)-methyl 3-cyanoacrylate gives similar results. Compounds **A** and **B** of **7b** are isomeric to products in the ribose series prepared by *Kozikowski et al.* by a different entry and used as intermediates in a synthesis of racemic showdomycin [5].



Scheme 4

Conversion of **6b/7b** to apioshowdomycin (**2**) was accomplished in analogy to the methods developed by *Kozikowski et al.* [5]. The mixture of the three diastereomers was transformed using Na_2CO_3/H_2O_2(30%)/H_2O/acetone to substituted succinimides **11** with a diastereomeric ratio of 71:29 in yields varying from 35–52% (Scheme 4). Some starting material could be recovered. The configuration at the anomeric centres of **11** is β in both cases ($J_{1,2} = 2.5$ and 3.4 Hz) as expected. The C–C double bond is introduced by treating succinimides **11** with 5 equiv. of lithium cyclohexyl(isopropyl)amide at −78°C followed by addition of 3 equiv. of phenylselenyl chloride. The selenides were oxidized with sodium metaperiodate to

selenoxides which eliminate phenyl selenenic acid to afford maleimide **12** as a homogenous single isomer with β-configuration ($J_{1,2} = 1.5$ Hz) which is identical with an authentic sample prepared in the course of the first synthesis of the apio analogue of showdomycin [3]. The yield of 26% for **12** resisted improvement, although 56% of starting material were recovered. Deprotection with CF_3CO_2H/H_2O (4:1) finally gave deprotected apioshowdomycin (**2**) in 44% yield [3].

(*E*)-Methyl 3-cyanoacrylate (**4**) is a useful doubly activated olefin for radical based C-C bond formation. The reaction products can be manipulated to give substituted succinimides, which might be applied to the synthesis of analogues of showdomycin with ribose replaced by other sugar components.

Experimental

For general remarks, see Ref. [3]. 2,3-O-Isopropylidene-*D*-apio-*D*-furanose was prepared as an anomeric mixture ($\alpha : \beta = 12 : 88$) by a literature procedure [10]. Pure β-anomer was obtained by flash chromatography (hexane/*EA* = 7:3; TLC: hexane/*EA* = 3:7; $R_f(\beta) = 0.5$, $R_f(\alpha) = 0.44$). MS spectra: Varian MAT 311 A with data system Varian V 72. Abbreviation used: *EA* = ethyl acetate.

(E)-Methyl 3-cyanoacrylate (**4**)

Phosphorus oxychloride (5.66 g, 3.43 ml, 36.9 mmol, 1.5 equiv.) [7] was added dropwise to a stirred suspension of fumaric methyl ester amide **3** (3.17 g, 24.6 mmol) [6] in dry pyridine (24 ml) at 0°C. After 1 h the ice bath was removed and the solution was allowed to warm up to room temperature. Ice and, after stirring for 30 min, $CHCl_3$ (30 ml) were added. The aqueous layer was extracted 6 times with $CHCl_3$. The combined organic phases were washed with 2 *N* HCl and water, dried (Na_2SO_4), and the solvent was removed under reduced pressure. Sublimation (35–40°C/8 mm) of the residue gave 3-cyanoacrylate **4** (2.17 g, 79%).

M.p.: 27–29°C; IR (Si): $\nu = 2229$, 1732, 1633, 1440, 1318, 1273, 1203, 1180, 1013 cm^{-1}; MS: *m/z* (%) = 111 (M^+, 2) 80 (100), 59 (2), 52 (35); ^1H NMR ($CDCl_3$): $\delta = 3.85$ (s, 3H, $COOCH_3$), 6.30 (d, $J = 16.2$ Hz, 1H, CH), 6.71 (d, $J = 16.2$ Hz, 1H, CH) ppm.

3′-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-D-apio-D-furanose (**9**)

To a stirred solution of 2,3-O-isopropylidene-*D*-apio-*D*-furanose (0.4 g, 2.11 mmol; $\alpha:\beta = 12:88$) [10], imidazole (0.344 g, 5.05 mmol, 2.4 equiv.), and a catalytic amount of 4-dimethylaminopyridine (*DMAP*) in dry *DMF* (7 ml), 0.695 g (0.66 ml, 2.53 mmol, 1.2 equiv.) *TBDPS*Cl were added under argon at 0°C. The mixture was stirred for 3–4 h at 0°C and then kept in a refrigerator at 4°C until all starting material was consumed (TLC, hexane/*EA*, 3:1). The solvent was removed by bulb to bulb distillation (40°C/0.1 mm), and dichloromethane (10 ml) and water (7 ml) were added to the residue. The organic phase was separated, and the aqueous one was extracted with dichloromethane (3 × 7 ml). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was flash chromatographed (hexane/*EA*, 10:1) to give **9** (0.750 g, 83%; $R_f = 0.65$ (hexane/*EA*, 3:1)) and disilylated compound (0.226 g, 16%; $R_f = 0.95$ (hexane/*EA*, 3:1)) as sirups.

$[\alpha]_D^{20} = -13.20$ ($c = 2.31$, $CHCl_3$); IR (Si): $\nu = 3424$, 2934, 2858, 1428, 1371, 1112 cm^{-1}; ^1H NMR ($CDCl_3$): mixture of anomers ($\alpha:\beta = 25 : 75$); $\delta = 0.99$ (s, 9H, $C(CH_3)_3$, α), 1.01 (s, 9H, $C(CH_3)_3$, β), 1.22 (s, 3H, $C(CH_3)_2$, β), 1.25 (s, 3H, $C(CH_3)_2$, α), 1.40 (s, 3H, $C(CH_3)_2$, β), 1.45 (s, 3H, $C(CH_3)_2$, α), 3.14 (brs, 1H, OH, β), 3.68 (AB system, $J = 10.3$ Hz, 3′-H, α), 3.72 (AB system, $J = 10.3$ Hz, 4-H, α), 3.73 (AB system, $J = 10.3$ Hz, 3′-H, β), 3.81 (brd, $J = 12.0$ Hz, 1H,

OH, *α*), 3.99 (AB system, $J = 9.9$ Hz, 4-H, *β*), 4.33 (d, $J = 3.0$ Hz, 1H, 2-H, *α*), 4.36 (s, 1H, 2-H, *β*), 4.99 (dd, $J = 3.0$, 12.0 Hz, 1H, 1-H, *α*), 5.31 (brs, 1H, 1-H, *β*), 7.34, 7.59 (2m, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): 19.18 ($C(CH_3)_3$), 26.78 ($C(CH_3)_3$, *β*), 26.82 ($C(CH_3)_3$, *α*), 27.14, 27.51 ($C(CH_3)_2$, *β*) 27.45, 27.57 ($C(CH_3)_2$, *α*), 64.66 (C-3′, *α*), 65.42 (C-3′, *β*), 70.28 (C-4, *α*), 74.07 (C-4, *β*), 81.54 (C-2, *α*), 87.30 (C-2, *β*), 91.22 (C-3, *α*), 91.47 (C-3, *β*), 98.16 (C-1, *α*), 101.75 (C-1, *β*), 113.26 ($C(CH_3)_2$, *β*), 114.26 ($C(CH_3)_2$, *α*), 127.84, 127.86, 129.98, 130.00, 132.31, 132.53, 132.67, 135.53, 135.56, 135.60, 135.70 (C_{arom}) ppm; – $C_{24}H_{32}O_5Si$ (428.60); calc.: C 67.26, H 7.53; found: C 66.90, H 7.33.

1-O-Benzoyl-3′-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-D-apio-D-furanose (**10**)

Benzoyl chloride (0.193 g, 0.16 ml, 1.37 mmol, 1.2 equiv.) was added dropwise to a stirred solution of compound **9** (0.486 g, 1.14 mmol; $\alpha : \beta = 25 : 75$) and dry pyridine (0.45 g, 0.46 ml, 5.7 mmol, 5 equiv.) in dry dichloromethane (10 ml) under argon; stirring was continued at room temperature for 20 h (TLC, hexane/*EA*, 5:1). The reaction mixture was poured into ice/water and extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed successively with diluted hydrochloric acid, a saturated aqueous solution of $NaHCO_3$, and water and then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography using hexane/*EA* (20:1) as eluent to afford benzoate **10** (0.569 g, 94%; $\alpha:\beta = 72:28$) with $R_f = 0.69$ (hexane/*EA*, 7:1) as a syrup.

$[\alpha]_D^{20} = -4.2$ ($c = 1.35$, $CHCl_3$); IR (Si): $\nu = 2932$, 2859, 1732, 1428, 1371, 1270, 1106 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 0.97$ (s, 9H, $C(CH_3)_3$, *β*), 1.02 (s, 9H, $C(CH_3)_3$, *α*), 1.29 (s, 3H, $C(CH_3)_2$, *α*), 1.33 (s, 3H, $C(CH_3)_2$, *β*), 1.42 (s, 3H, $C(CH_3)_2$, *α*), 1.47 (s, 3H, $C(CH_3)_2$, *β*), 3.72 (AB system, $J = 10.8$ Hz, 3′-H, *α*), 3.79 (AB system, $J = 10.8$ Hz, 3′-H, *β*), 3.96 (AB system, $J = 9.8$ Hz, 4-H, *α*), 4.08 (AB system, $J = 9.8$ Hz, 4-H, *β*), 4.68 (s, 1H, 2-H, *β*), 4.77 (d, $J = 4.0$ Hz, 1H, 2-H, *α*), 6.17 (d, $J = 4.0$ Hz, 1H, 1-H, *α*), 6.38 (s, 1H, 1-H, *β*), 7.26–8.05 (m, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.23$ ($C(CH_3)_3$), 26.74 ($C(CH_3)_3$, *β*), 26.84 ($C(CH_3)_3$, *α*), 27.72 ($C(CH_3)_2$, *α*), 27.79, 27.92 ($C(CH_3)_2$, *β*), 28.34 ($C(CH_3)_2$, *α*), 64.93 (C-3′, *β*), 65.27 (C-3′, *α*), 73.26 (C-4, *α*), 75.88 (C-4, *β*), 82.31 (C-2, *α*), 86.44 (C-2, *β*), 91.25 (C-3, *α*), 92.25 (C-3, *β*), 98.49 (C-1, *α*), 102.68 (C-1, *β*), 114.06 ($C(CH_3)_2$, *β*), 116.28 ($C(CH_3)_2$, *α*), 127.80, 127.85, 128.37, 129.80, 129.91, 129.97, 132.67, 132.77, 133.28, 135.53, 135.58, 135.65 (C_{arom}), 165.00 (CO) ppm; $C_{31}H_{36}O_6Si$ (532.71); calc.: C 69.90, H 6.81; found: C 70.13, H 7.01.

3′-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-D-apio-β-D-furanosyl bromide (**5b**)

Benzoate **10** (0.419 g, 0.788 mmol) was dried first by coevaporation with dry toluene and then *in vacuo* (0.1 mm). Dichloromethane (5 ml), bromotrimethylsilane (0.482 g, 0.41 ml, 3.15 mmol, 4 equiv.), and trimethylsilyl triflate (0.052 g, 0.043 ml, 0.236 mmol, 0.3 equiv.) were added, and the solution was stirred for 20 h at 20–24°C in a flask protected against light (when the room temperature was higher than 20–24°C and the reaction time longer, the yield dropped). The reaction mixture was poured onto an ice-cold saturated aqueous solution of $NaHCO_3$ and the organic phase was separated. The aqueous layer was extracted with dichloromethane (3 × 10 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to furnish crude bromide **5b** (0.367 g, 95%) which was homogenous by ^1H NMR spectroscopy and was used immediately after preparation for the next step. It hydrolyzed partly during TLC (hexane/*EA*, 10:1).

IR (Si): $\nu = 3072$, 2933, 2858, 1778, 1462, 1428, 1371, 1242, 1112 cm^{-1}; ^1H NMR (benzene-d_6): $\delta = 1.14$ (s, 9H, $C(CH_3)_3$), 1.27 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 3.87 (AB system, $J = 11.1$ Hz, 3′-H), 4.00 (AB system, $J = 10.5$ Hz, 4-H), 4.84 (s, 1H, 2-H), 6.38 (s, 1H, 1-H), 7.20–7.83 (m, $10H_{arom}$) ppm; ^{13}C NMR (benzene-d_6): $\delta = 20.13$ ($C(CH_3)_3$), 27.61 ($C(CH_3)_3$), 28.37, 28.41 ($C(CH_3)_2$), 67.27 (C-3′), 77.98 (C-4), 91.80 (C-2), 92.84 (C-3), 96.62 (C-1), 114.60 ($C(CH_3)_2$),

128.87, 128.90, 130.88, 130.92, 133.80, 134.02, 136.65, 136.84 (C_{arom}) ppm; $C_{24}H_{31}BrO_4Si$ (491.51); calc.: C 58.65, H 6.36; found: C 57.84, H 6.36.

Preparation of cyano esters **6a** *and* **7a**

Apiosyl bromide **5a** (0.518 g, 1.45 mmol) and a catalytic amount of *AIBN* were dissolved in dry benzene (10 ml) and reacted with (*E*)-methyl 3-cyanoacrylate (0.805 g, 7.25 mmol, 5 equiv.) in dry benzene (3.5 ml) and *tris*(trimethylsilyl)silane (0.98 ml, 3.19 mmol, 2.2 equiv.) in dry benzene (10 ml) according to a literature procedure [4]. The solution was refluxed under argon until the starting material was consumed (TLC, hexane/*EA*, 4:1, 2.5 h). After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/*EA*, 10:1, 7:1, 4:1) to give **6a** (0.077 g) with $R_f = 0.30$ and **7a** (0.400 g) with $R_f = 0.24$ (combined yield : 85%).

6a: $[\alpha]_D^{20} = +6.51$ ($c = 1.06$, $CHCl_3$); IR (Si): $\nu = 2990, 2956, 2248, 1724, 1602, 1585, 1452, 1373, 1315, 1270, 1176, 1105, 1026$ cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.43$, 1.54 (2s, 3H each, $C(CH_3)_2$), 2.76 (AB system, $J = 6.4$, 7.4, 16.7 Hz, CH_2COOCH_3), 3.26 (ddd, $J = 6.4$, 7.4, 9.4 Hz, 1H, CHCN), 3.73 (s, 3H, $COOCH_3$), 3.97 (AB system, $J = 10.3$ Hz, 4-H), 4.19 (dd, $J = 2.0$, 9.4 Hz, 1H, 1-H), 4.55 (AB system, $J = 12.0$ Hz, 3′-H), 4.74 (d, $J = 2.0$ Hz, 1H, 2-H), 7.48, 7.60, 8.08 (m, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 27.58$, 27.82 ($C(CH_3)_2$), 29.15 (*C*HCN), 33.54 (CH_2COOCH_3), 52.40 ($COOCH_3$), 64.71 (C-3′), 74.77 (C-4), 84.64, 85.71 (C-1, C-2), 90.67 (C-3), 115.14 ($C(CH_3)_2$), 118.40 (CN), 128.61, 129.26, 129.71, 133.46 (C_{arom}), 166.02 (CO), 169.82 ($COOCH_3$) ppm; $C_{20}H_{23}NO_7$ (389.41); calc.: C 61.69, H 5.95, N 3.60; found: C 61.30, H 6.12, N 3.82.

7a: $[\alpha]_D^{20} = -8.89$ ($c = 0.585$, $CHCl_3$); IR (Si): $\nu = 3063, 2989, 2955, 2880, 2251, 1731, 1601, 1584, 1492, 1452, 1372, 1106$ cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.39$, 1.51 (2s, 3H each, $C(CH_3)_2$, **C**), 1.41, 1.52 (2s, 3H, each, $C(CH_3)_2$, **A**), 1.41, 1.53 (2s, 3H each, $C(CH_3)_2$, **B**), 2.71 (AB system, $J = 5.4$, 7.4, 16.7 Hz, CH_2CN, **A**), 2.72 (AB system, $J = 6.4$, 7.9, 17.2 Hz, CH_2CN, **B**), 2.79 (AB system, $J = 6.4$, 7.4, 17.2 Hz, CH_2COOCH_3, **C**), 2.89 (ddd, $J = 5.4$, 7.4, 9.6 Hz, 1H, $CHCOOCH_3$, **A**), 3.05 (dt, $J = 6.4$, 7.9 Hz, 1H, $CHCOOCH_3$, **B**), 3.33 (ddd, $J = 4.4$, 6.4, 7.4 Hz, 1H, CHCN, **C**), 3.72 (s, 3H, $COOCH_3$, **C**), 3.74 (s, 3H, $COOCH_3$, **B**), 3.75 (s, 3H, $COOCH_3$, **A**), 3.93 (AB system, $J = 10.4$ Hz, 4-H, **A**), 3.94 (AB system, $J = 10.3$ Hz, 4-H, **B**), 4.07 (AB system, $J = 9.8$ Hz, 4-H, C), 4.13 (dd, $J = 3.4$, 4.4 Hz, 1H, 1-H, **C**), 4.17 (dd, $J = 2.0$, 9.6 Hz, 1H, 1-H, **A**), 4.18 (dd, $J = 3.0$, 6.4 Hz, 1H, 1-H, **B**), 4.46 (AB system, $J = 11.8$ Hz, 3′-H, **B**), 4.50 (AB system, $J = 11.8$ Hz, 3′-H, **A**), 4.60 (AB system, $J = 11.8$ Hz, 3′-H, **C**), 4.64 (d, $J = 2.0$ Hz, 1H, 2-H, **A**), 4.65 (d, $J = 3.5$ Hz, 1H, 2-H, **C**), 4.73 (d, $J = 3.0$ Hz, 1H, 2-H, **B**), 7.45, 7.57, 8.04 (m, H_{arom}; **A**, **B**, **C**) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 16.97$ (CH_2CN, **A**), 17.26 (CH_2CN, **B**), 27.77, 28.24 ($C(CH_3)_2$, **B**), 27.79, 27.82 ($C(CH_3)_2$, **A**), 27.82, 28.20 ($C(CH_3)_2$, **C**), 31.12 (*C*HCN, **C**), 33.51 (CH_2COOCH_3, **C**), 43.10 (*C*-$HCOOCH_3$, **A**), 44.06 ($CHCOOCH_3$, **B**), 52.43 ($COOCH_3$, **C**), 52.74 ($COOCH_3$, **B**), 52.89 (COO-CH_3, **A**), 64.86 (C-3′, **C**), 64.95 (C-3′, **A**), 65.14 (C-3′, **B**), 74.32 (C-4, **A**), 75.30 (C-4, **B**), 75.70 (C-4, **C**), 84.05, 85.53 (C-1, C-2, **C**), 84.43, 85.70 (C-1, C-2, **A**), 84.73, 85.33 (C-1, C-2, **B**), 90.56 (C-3, **A**), 90.78 (C-3, **B**), 91.03 (C-3, **C**), 114.99 ($C(CH_3)_2$, **A**), 115.76 ($C(CH_3)_2$, **B**), 115.84 ($C(CH_3)_2$, **C**), 117.08 (CN, **B**), 117.23 (CN, **A**), 118.68 (CN, **C**), 128.46, 128.58, 128.61, 129.30, 129.42, 129.62, 129.66, 129.74, 133.26, 133.43, 133.52 (C_{arom}), 166.07, 166.18 (CO), 170.04, 170.18 ($COOCH_3$) ppm; $C_{20}H_{23}NO_7$ (389.41); calc.: C 61.69, H 5.95; found: C 62.02, H 5.96.

Preparation of cyano esters **6b** *and* **7b**

Apiosyl bromide **5b** (0.344 g, 0.7 mmol) and a catalytic amount of *AIBN* in dry benzene (16 ml) were reacted with (*E*)-methyl cyanoacrylate (**4**; 0.389 g, 3.51 mmol, 5 equiv.) in dry benzene (4 ml) and *tris*(trimethylsilyl)silane (0.47 ml, 1.54 mmol, 2.2 equiv.) in dry benzene (5 ml) according to a literature procedure [4]. The solution was refluxed under argon until the starting material was

consumed (TLC, hexane/*EA*, 10:1, 2 h). After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/*EA*, 10:1) to give **6b** (0.048 g, $R_f = 0.30$) and **7b** (0.295 g, $R_f = 0.25$) in a combined yield of 94%.

6b: $[\alpha]_D^{20} = -16.8$ ($c = 0.75$, $CHCl_3$); IR (Si): $\nu = 3073$, 2933, 2859, 2245, 1744, 1590, 1462, 1440, 1428, 1371, 1216, 1113, 998 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.09$ (s, 9H, $C(CH_3)_3$), 1.28, 1.46 (2s, 3H each, $C(CH_3)_2$), 2.70 (AB system, $J = 6.4$, 7.4, 16.7 Hz, CH_2COOCH_3), 3.24 (ddd, $J = 6.4$, 7.4, 10.3 Hz, 1H, CHCN), 3.70 (s, 3H, $COOCH_3$), 3.72 (AB system, $J = 10.8$ Hz, 3′-H), 3.86 (AB system, $J = 10.3$ Hz, 4-H), 4.16 (dd, $J = 1.0$, 10.3 Hz, 1H, 1-H), 4.71 (d, $J = 1.0$ Hz, 1H, 1H, 2-H), 7.41, 7.66 (m, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.16$ ($C(CH_3)_3$), 26.89 ($C(CH_3)_3$), 27.59, 27.68 ($C(CH_3)_2$), 28.47 (*C*HCN), 33.62 (CH_2COOCH_3), 52.27 ($COOCH_3$), 64.28 (C-3′), 74.04 (C-4), 84.87, 85.92 (C-1, C-2), 92.40 (C-3), 113.99 ($C(CH_3)_2$), 118.61 (CN), 127.94, 127.96, 130.05, 130.06, 132.29, 132.36, 135.58, 135.69 (C_{arom}), 169.82 ($COOCH_3$) ppm; $C_{29}H_{37}NO_6Si$ (523.71); calc.: C 66.51, H 7.12, N 2.67; found: C 66.45, H 6.81, N 2.57.

7b: $[\alpha]_D^{20} = -25.12$ ($c = 2.5$, $CHCl_3$); IR (Si): $\nu = 3072$, 3050, 2933, 2859, 2250, 1743, 1692, 1589, 1440, 1428, 1370, 1246, 1215, 1113, 998 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.05$ (s, 9H, $C(CH_3)_3$, **C**), 1.07 (s, 9H, $C(CH_3)_3$, **B**), 1.09 (s, 9H, $C(CH_3)_3$, **A**), 1.31, 1.47 (s, 3H each, $C(CH_3)_2$, **B**), 1.34, 1.48 (s, 3H each, $C(CH_3)_2$, **A**), 1.37, 1.51 (s, 3H each, $C(CH_3)_2$, **C**), 2.56 (AB system, $J = 5.4$, 8.9, 17.2 Hz, CH_2CN, **A**), 2.66 (AB system, $J = 4.9$, 7.9, 16.7 Hz, CH_2CN, **B**), 2.72 (AB system, $J = 6.4$, 8.1, 17.2 Hz, CH_2COOCH_3, **C**), 2.95 (m, 2 × 1H, *C*HCOOCH$_3$, **A**, **B**), 3.26 (dt, $J = 5.9$, 7.9 Hz, 1H, CHCN, **C**), 3.70 (s, 3H, $COOCH_3$, **A**), 3.72 (s, 3H, $COOCH_3$, **C**), 3.76 (s, 3H, $COOCH_3$, **B**), 3.61–4.05 (6 overlapping AB systems, 3′-H, 4-H, **A**, **B**, **C**), 4.06 (dd, $J = 2.5$, 8.4 Hz, 2 × 1H, 1-H, **A**, **C**), 4.14 (dd, $J = 1.5$, 10.8 Hz, 1H, 1-H, **B**), 4.43 (d, $J = 2.5$ Hz, 1H, 2-H, **A**), 4.50 (d, $J = 3.0$ Hz, 1H, 2-H, **C**), 4.67 (d, $J = 1.5$ Hz, 1H, 2-H, **B**), 7.40, 7.65 (m, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 16.83$ (CH_2CN, **B**), 16.92 (CH_2CN, **A**), 19.18, 19.23 ($C(CH_3)_3$), 26.86, 26.88 ($C(CH_3)_3$), 27.71, 27.79 ($C(CH_3)_2$, **B**), 27.92, 28.35 ($C(CH_3)_2$, **C**), 28.01, 28.14 ($C(CH_3)_2$, **A**), 30.97 (*C*HCN, **C**), 33.57 (CH_2COOCH_3, **C**), 42.63 (*C*HCOOCH$_3$, **B**), 43.73 (*C*HCOOCH$_3$, **A**), 52.39 ($COOCH_3$, **C**), 52.56 ($COOCH_3$, **A**), 52.74 ($COOCH_3$, **B**), 64.46 (C-3′, **B**), 64.65 (C-3′, **A**), 64.86 (C-3′, **C**), 73.72 (C-4, **B**), 74.67 (C-4, **A**), 75.37 (C-4, **C**), 84.17, 84.89 (C-1, C-2, **C**), 84.38, 86.02 (C-1, C-2, **B**), 84.77, 85.43 (C-1, C-2, **A**), 92.44 (C-3, **B**), 92.83 (C-3, **A**), 93.12 (C-3, **C**), 113.90, 114.92 ($C(CH_3)_2$), 116.89, 117.40 (CN), 127.78, 127.89, 127.92, 129.79, 129.90, 130.01, 130.09, 130.12, 132.34, 132.52, 132.55, 132.70, 135.52, 135.54, 135.57, 135.64, 135.71, 135.75 (C_{arom}), 169.69 ($COOCH_3$, **C**), 170.38 ($COOCH_3$, **A**), 170.51 ($COOCH_3$, **B**) ppm; $C_{29}H_{37}NO_6Si$ (523.71); calc.: C 66.51, H 7.12, N 2.67; found: C 66.54, H 6.83, N 2.63.

Cyclization of mixture **6b/7b**

To a stirred solution of a mixture of diastereomeric cyano esters **6b/7b** (0.131 g, 0.25 mmol) in analytical grade acetone (2.8 ml), hydrogen peroxide (30%, 0.73 ml), water (0.48 ml), and a 0.5 *M* aqueous Na_2CO_3 solution (0.39 ml) were added at room temperature [5]. Vigorous stirring was continued as long as the amount of starting material was decreasing in the reaction mixture as judged by TLC (hexane/*EA*, 5:1; 24–65 h). After addition of ethyl acetate (5 ml) and stirring for 10 min, water (5 ml) was added. The organic layer was separated, and the aqueous one was extracted with ethyl acetate (3 × 5 ml). The combined organic phases were washed successively with water (5 ml), a solution of $NaHSO_3$ (0.423 g) in water (5 ml), again with water (5 ml), and were then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was flash chromatographed (hexane/*EA*, 10:1, 4:1) to give starting material (0.018 g, 14%) and succinimide **12** (0.066 g, 52%) with $R_f = 0.30$ (hexane/*EA*, 3:1).

IR (Si): $\nu = 3072$, 2986, 2932, 1778, 1716, 1428, 1371, 1243, 1186, 1114 cm^{-1}; ^1H NMR ($CDCl_3$): two diastereomers **A** and **B** (71:29) $\delta = 0.99$, 1.07 (2s, 9H each, $C(CH_3)_3$, **A**, **B**), 1.28, 1.44 (2s, 3H each, $C(CH_3)_2$, **A**), 1.31, 1.47 (2s, 3H each, $C(CH_3)_2$, **B**), 2.58 (AB system, $J = 5.5$, 8.2, 18.7 Hz, CH_2CO, **A**), 2.65 (AB system, $J = 4.9$, 8.9, 18.7 Hz, CH_2CO, **B**), 3.06 (dt, $J = 5.5$, 8.2 Hz, 1H,

CHCO, **A**), 3.08 (dt, $J = 4.9$, 8.9 Hz, 1H, CHCO, **B**), 3.70 (AB system, $J = 10.8$ Hz, 3″-H, **A**), 3.72 (AB system, $J = 10.8$ Hz, 3″-H, **B**), 3.78 (AB system, $J = 10.8$ Hz, 4′-H, **A**), 3.84 (AB system, $J = 9.9$ Hz, 4′-H, **B**), 4.05 (dd, $J = 3.4$, 4.9 Hz, 1H, 1′-H, **B**), 4.15 (dd, $J = 2.7$, 8.2 Hz, 1H, 1′-H, **A**), 4.76 (d, $J = 2.7$ Hz, 1H, 2′-H, **A**), 4.78 (d, $J = 3.4$, 1H, 2′-H, **B**), 7.30, 7.60 (2m, H_{arom}), 8.28 (brs, 1H, NH, **B**), 8.42 (brs, 1H, NH, **A**) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.22$ ($C(CH_3)_3$, **A**), 19.27 ($C(CH_3)_3$, **B**), 26.87 ($C(CH_3)_3$, **B**), 26.90 ($C(CH_3)_3$, **A**), 27.82, 28.08 ($C(CH_3)_2$, **A**), 27.94, 28.50 ($C(CH_3)_2$, **B**), 31.79 (CH_2CO, **A**), 33.55 (CH_2CO, **B**), 42.25 (CHCO, **A**), 42.81 (CHCO, **B**), 64.79 (C-3″, **A**), 65.19 (C-3″, **B**), 74.15 (C-4′, **A**), 75.29 (C-4′, **B**), 83.88, 85.85 (C-1′, C-2′, **B**), 84.01, 85.07 (C-1′, C-2′, **A**), 92.41 (C-3′, **A**), 93.15 (C-3′, **B**), 114.53 ($C(CH_3)_2$, **A**), 115.22 ($C(CH_3)_2$, **B**), 127.72, 127.87, 127.92, 129.73, 129.82, 129.98, 130.11, 132.40, 132.60, 132.86, 133.13, 135.52, 135.56, 135.65, 135.78 (C_{arom}), 175.86, 176.71 (CO, **B**), 175.97, 177.24 (CO, **A**) ppm; $C_{28}H_{35}NO_6Si$ (509.68); calc.: C 65.98, H 6.92, N 2.75; found: C 65.33, H 6.98, N 2.36.

2-(3″-O-tert-Butyldiphenylsilyl-2′,3′-O-isopropylidene-D-apio-β-D-furanosyl)-1H-pyrrole-2,5-dione (**12**)

A solution of BuLi (1.6 *N*, 0.86 ml, 1.37 mmol, 6 equiv.) in hexane was added at −20°C to a stirred solution of dry cyclohexyl(isopropyl)amine (0.161 g, 0.19 ml, 1.14 mmol, 5 equiv.) in dry *THF* (3 ml) under argon. After 15 min, the solution was cooled to −78°C, and succinimide **11** (0.116 g, 0.228 mmol) dissolved in dry *THF* (2.5 ml) was added dropwise, followed by a solution of phenylselenyl chloride (0.131 g, 0.68 mmol, 3 equiv.) in dry *THF* (1 ml after 20 min) [5]. The temperature was allowed to rise slowly to −20°C. $NaIO_4$ (0.316 g, 1.37 mmol, 6 equiv.) dissolved in a mixture of water/methanol (2/5 ml) was added, and the reaction mixture was allowed to warm up to room temperature overnight. Then, dichloromethane (7 ml) and water were added and stirring was continued for a few minutes. The organic layer was separated, and the aqueous one was extracted with dichloromethane (3 × 10 ml). The combined organic phases were washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography of the residue using hexane/*EA* (at the beginning 10:1, then 4:1) as eluent yielded starting material (65 mg, 65%) and maleimide **12** (30 mg (26%), $R_f = 0.51$ (hexane/*EA*, 3:1), $[\alpha]_D^{20} = -21.28$ ($c = 0.39$, $CHCl_3$)). The spectroscopic data are identical with the published ones of an authentic sample [3].

2-(D-Apio-β-D-furanosyl)-1H-pyrrole-2,5-dione (**2**)

A solution of substituted maleimide **12** (55 mg, 0.11 mmol) in trifluoroacetic acid/water (2/0.5 ml) was stirred at room temperature until no starting material was present (TLC, hexane/*EA*, 2:1, 2 h) [5]. The solution was concentrated *in vacuo*, and the residue was dried (0.5 mm) and purified by flash chromatography using at first hexane/*EA* (2:1), then *EA* as eluent to yield apioshowdomycin (**2**, 11 mg (44%), $R_f = 0.55$ (*EA*/MeOH, 10:1)) identical in all respects with an authentic sample [3].

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