Bis-Tetrahydrofurans from Carbohydrates via Iodoetherification and Iodine Substitution

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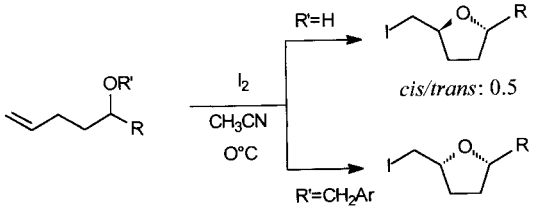
Abstract: Iodocyclization followed by nucleophilic displacement of iodine affords mainly *trans*-2,5-substituted THF related to annonaceous acetogenins.

Key words: carbohydrates, bis-tetrahydrofurans, iodoetherification, nucleophilic displacement of iodine, *trans*-2,5-disubstituted tetrahydrofurans

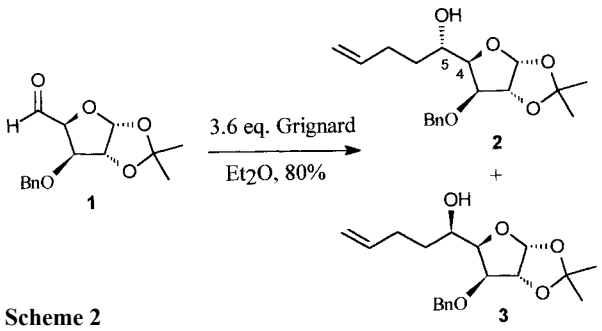
The synthesis of 2,5-disubstituted tetrahydrofurans (THF) was initially studied in connection with the chemistry of ionophore antibiotics.[1] This interest has now been renewed because of the potent cytotoxic, pesticidal and immunosuppressive activities demonstrated by most members of the large family (over 280) of recently isolated annonaceous acetogenins.[2] Among the available metho-dologies reviewed by Figadère[3] and Boivin,[4] the iodocyclization of γ,δ-unsaturated alcohols and ethers pioneered by Bartlett[5] is particularly worthy of note for the selective preparation of *trans*- and *cis*-2,5-disubstituted THF lacking other ring substituents (Scheme 1).



Scheme 1

This methodology has been applied by Mootoo for both the cyclization of carbohydrate derivatives[6,7] and γ,δ-unsaturated acetonides[8] and by Brimble[9] for the preparation of bis-THF compounds from mono-THF ones. These recent reports prompt us to describe, as part of an ongoing project on the synthesis of tetrahydrofuran acetogenins and analogues from carbohydrates,[10–13] the iodocyclization of γ,δ-unsaturated alcohols derived from D-glucose and the attempted nucleophilic displacement of the intermediate iodo derivatives. The latter reaction has not been reported in detail in the literature since most compounds obtained by iodocyclization have been reduced.[4,5] This strategy could be an alternative to the preparation of bis-THF through epoxidation–cyclization which has been described previously for similar γ,δ-unsaturated alcohols and shown to generate a 1:1 mixture of *cis*- and *trans*-THF.[10,12] It was thus expected that this sequence of reaction would give the *trans*-THF (this isomer being more common among bioactive acetogenins than the *cis* one) with higher selectivity.

Unsaturated alcohols **2** (5*S*) and **3** (5*R*) were prepared from the known aldehyde **1**[13] and the Grignard reagent of 3-bromobut-1-ene in a 4:1 ratio in THF and in a 2:1 ratio in diethyl ether (Scheme 2).[14–17] These compounds were easily separated by flash chromatography and characterized by ^{1}H NMR in agreement with literature data for similar alcohols derived from **1**.[10,14–16] Iodocyclization was first studied with the major isomer **2** since the *threo* configuration between C-4 and C-5 is similar to the one prevailing for most adjacent acetogenins (Scheme 3).



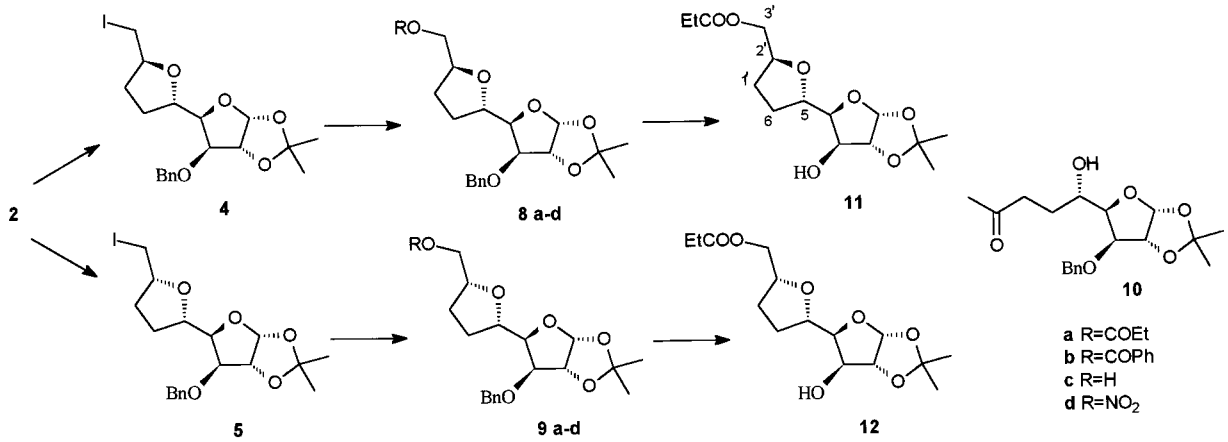
Scheme 2

Table 1 Iodocyclization of Alkene **2**

Conditions[a]	Yield (%)[b]	*trans*/*cis* ratio
A, CH_3CN, 0 °C	86	76:24
A, Et_2O/H_2O (5:2), 0 °C	80	81:19
A, DMF, 20 °C	72	77:23
A, CH_2Cl_2, 20 °C	69	54:46
A, THF, 20 °C	54	73:27
B, CH_2Cl_2/THF (4:1), 20 °C	71	69:31

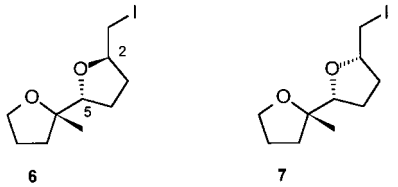
[a] A: I_2-$NaHCO_3$ (3.2 equiv), 1 h B: NIS (2 equiv), 30 min.
[b] Overall isolated yield for the mixture of iodides **4**/**5** after flash chromatography.

The ratio of *trans*- and *cis*-iodides was determined by HPLC and the results are reported in Table 1. In each case, except in CH_2Cl_2 as solvent, a major isomer was obtained with an optimal ratio of 4:1 observed in the biphasic water/diethyl ether mixture. At this point, ^{1}H NMR data of the **4**/**5** mixture did not allow us to confirm the predominant formation of the *trans* isomer. Such a determination has been done by Brimble[9] by comparison of the H-2 and H-5 chemical shifts, according to the Cassady model,[18] for compounds **6** and **7**. In our case these protons are hidden by those of the carbohydrate moiety. Indeed, the CH_2I protons appear in our case at similar figures (δ = 3.15 and



Scheme 3

3.36) for both compounds in agreement with the reported values for **6** (δ = 3.18 and 3.28) and **7** (δ = 3.18 and 3.25). Similarly, ^{13}C NMR data did not provide conclusive evidence for iodide configuration: two CH_2I signals at δ = 10.1 and 10.5 were observed in a 5:1 ratio (as compared to 4:1 in HPLC), while Brimble[9] has reported δ = 10.2 and 10.7 respectively for **7** and **6**. However, as it will be demonstrated later, this similarity would have lead to a wrong attribution of a *cis* configuration to the major isomer.



6 **7**

The mixture of iodo derivatives **4** and **5** was then treated with various oxygen nucleophiles (Table 2) since their separation could be efficiently carried out only on an analytical scale. The use of either cesium propionate (either pure or generated in situ[19]) or cesium benzoate,[20] or potassium superoxide,[21] or TBAN[22] (tetrabutylammonium nitrate), respectively led to the formation of inseparable mixtures of esters, alcohols and nitrates, together with ketone **10**. The structure of the latter was easily characterized by IR; ν = 1719 cm^{-1}, ^1H NMR: δ = 2.14 (3H, s) and ^{13}C NMR: δ = 209.3. However at this stage the **8**/**9** ratio could not be determined by ^1H NMR since no significant difference was observed between the CH_2O protons for all isomeric pairs.

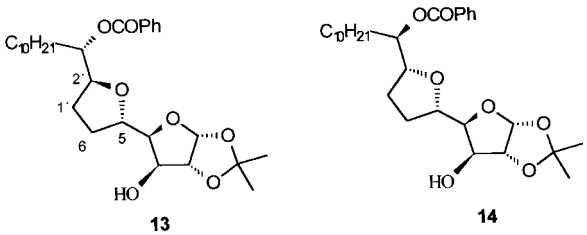
As we have shown before,[10,12] Pd/C catalyzed hydrogenolysis of the benzyl group of compounds **8a**, **9a** (80:20) gave an easily separable (flash chromatography) mixture of alcohols **11** and **12** (75:25 ratio, 95% overall yield). At this stage H-5 and H-2' chemical shifts (unambiguously determined using ^1H–^1H COSY) were compared to those previously observed for compounds **13** and **14** whose structures have been earlier confirmed by chemical correlation (Table 3).[10] As expected, H-2' was slightly more deshielded (Δδ +0.11 ppm) for the *trans*-isomer **11**

Table 2 Nucleophilic Displacement of a 4:1 Mixture of *trans* and *cis* Iodo Derivatives **4** and **5**

Conditions	Product Distribution (Yield, %)[b]	Ratio[c]
$EtCO_2H$, Cs_2CO_3 (10 equiv), DMF[a]	**8a**, **9a** (56) **10** (41.5)	57:43
$EtCO_2H$, Cs_2CO_3 (1.5 equiv), DMF	**8a**, **9a** (24) **10** (17)	58:42
$EtCO_2Cs$ (1 equiv), DMF	**8a**, **9a** (45) **10** (45)	50:50
$EtCO_2Cs$ (10 equiv), DMF	**8a**, **9a** (65) **10** (28)	69:31
$EtCO_2Cs$ (10 equiv), THF	**8a**, **9a** (26) **10** (31)	46:54
$PhCO_2H$, CsF, DMF, 60 °C	**8b**, **9b** (49) **10** (36)	58:42
KO_2 (3 equiv), 18-crown-6, DMSO, rt	**8c**, **9c** (61) **10** (31)	66:34
TBAN (1.5 equiv), toluene, 80 °C	**8d**, **9d** (55) **10** (26)	68:32

[a] Reactions with $EtCO_2Cs$ carried out at 60 °C.
[b] Isolated yield after flash chromatography.
[c] Ratio between compounds arising from nucleophilic substitution (**8** and **9**) and elimination (**10**).

(Δδ +0.18 ppm for **13**) with respect to the *cis* one. This was also in agreement with the Cassady model (Δδ +0.12 ppm reported between *threo-trans-threo* and *threo-cis-threo* model compounds).[20] Interestingly, similar chemical shifts were observed for H-6 and H-1' for the *trans* compounds **11** and **13** and for the *cis* ones **12** and **14** (see Table 3), although no attribution is possible between these protons (even by comparison with the model compounds of Fujimoto[23]).



13 **14**

This result confirmed the favored formation of the *trans*-isomer in the iodocyclizations reported herein and led us to study the behavior of the isomeric alcohol **3**. Upon treatment with I_2, **3** afforded a mixture of iodo derivatives **15** and **16** in good yield (acetonitrile: 90%; diethyl ether/

Table 3 Selected ^{1}H NMR Data of Alcohols **11**, **12**, **13** and **14**

Proton[a]	**11**	**12**	**13**	**14**
H-5	4.47	4.48	4.52	4.44
H-8	4.36	4.25	4.32	4.14
H-6, H-1'	3H, 2.15	2H, 2.12	3H, 2.14	2H, 2.13
	1H, 1.63	2H, 1.92	1H, 1.70	2H, 1.91

[a] All signals appear as multiplets.

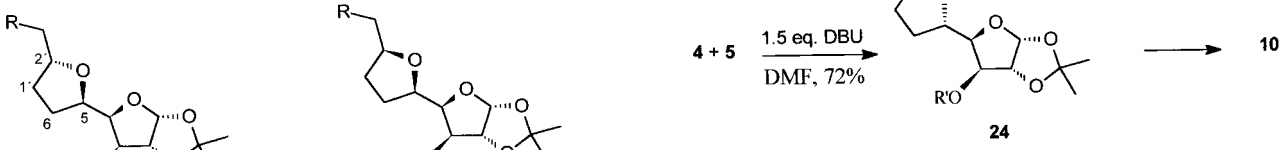
Table 4 Selected ^{1}H NMR Data of Alcohols **20**, **21**, **22** and **23**

Proton[a]	**20**	**21**	**22**	**23**
H-5	4.28	4.18	4.28	4.10
H-8	4.28	4.33	4.14	4.10
H-6, H-1'	1H, 2.22	1H, 2.16	1H, 2.22	2H, 2.10
	1H, 2.15	1H, 2.08	1H, 2.15	
	1H, 1.85	1H, 1.95	2H[b]	2H[b]
	1H, 1.75	1H, 1.82	1.7–1.9	1.8–2.0

[a] All signals appear as multiplets.
[b] Partly hindered with H-4'.

water: 85%). However no separation was observed in HPLC and, as in the case of **4** and **5**, ^{1}H and ^{13}C NMR data did not allow us to determine their relative configurations. Indeed, two signals at δ = 10.5 and 10.2 in a 2.5:1 ratio were observed, thereby indicating a lower selectivity compared to **4** and **5**. Upon treatment with in situ generated $EtCO_2Cs$ in DMF, a 58:42 mixture of esters **17**, **18** and ketone **19** was obtained. Hydrogenolysis of the ester mixture afforded alcohols **20** and **21** in a 70:30 ratio (after flash chromatography). Identification of **20** as the *trans*-isomer was carried out as described above by comparison of selected ^{1}H NMR data with those of the previously reported **22** and **23**.[12] Furthermore in the case of *erythro-trans-threo* (or *erythro*) and *erythro-cis-threo* (or *erythro*) configurations, a deshielding of *ca*. 0.10 ppm (*trans* vs. *cis*) has also been reported by Cassady. Such a deshielding (Δδ +0.10 ppm) was observed for H-5 but not for H-2' (Δδ –0.05 ppm) for **20** and **21 (**the latter may result from different side chain conformations in both isomers). Although H-6 and H-1' were partly hindered in the case of **22** and **23**, their chemical shifts were similar respectively to those of **20** and **21**.

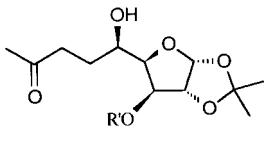
In conclusion, iodocyclization followed by nucleophilic displacement of iodine allows the preparation of a 2,5-disubstituted THF from alcohols **2** and **3**, with a *trans/cis* selectivity of about 3:1 (instead of a 1:1 ratio obtained using epoxidation–cyclization). This is in agreement with all reported examples of iodocyclization of γ,δ-unsaturated alcohols. Furthermore, a selective access toward *cis* compounds may also be considered by the method of Marek and Normant[24] through cyclization of the corresponding *tert*-butyl esters. However, this study shows that the nucleophilic substitution of iodine is always accompanied by the formation of a γ-hydroxy ketone. This has been previously observed in the silver carbonate treatment of **6** and **7** by Brimble,[9] who has suggested the intermediacy of a primary carbenium ion, after solvolysis of iodide, followed by hydride migration and hydrolysis. However the intermediate formation of the unstable enol ether **24** resulting from elimination should be considered since treatment of the **4**/**5** mixture with DBU (1.5 equiv) in DMF gives only ketone **10** (72%) (Scheme 4).



Scheme 4

15 R= I, R'= Bn
17 R= OCOEt, R'= Bn
20 R= OCOEt, R'= H

16 R= I, R'= Bn
18 R= OCOEt, R'= Bn
21 R= OCOEt, R'= H



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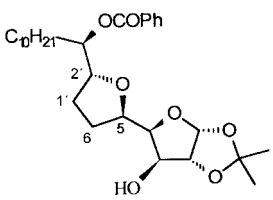

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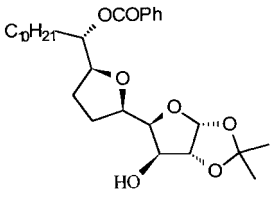

23

Overall, this methodology appears to be less diastereoselective than the Kennedy cyclization of homoallylic alcohols induced by rhenium derivatives.[25] Nevertheless, it offers a simple alternative which is however limited by the elimination process leading to ketone **10**. Finally, it should be pointed out that the intermediate (iodomethyl)tetrahydrofurans, which are very prone toward elimination, may be considered as good substrates to test new nucleophilic substitution conditions in the future.

Mps were recorded on a Buchi Tottoli 510 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance DPX 300 operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts are expressed in ppm positive values downfield from internal TMS. Elemental and MS analyses were measured by the Service Central d'Analyse du CNRS (Vernaison). Optical rotations were measured

on a Schmidt Polartronic HN8 polarimeter. IR spectra were recorded on a Nicolet Magna 750 FTIR spectrophotometer. All solvents were dried using standard methods. Separations were done under flash chromatography conditions on silica gel (Matrex, 25–40 mμ) and TLC were performed on silica gel plates (Merck, $60GF_{254}$). Analysis of iodide mixtures was carried by HPLC using a PhaseSep Spherisorb S5CN column (15 cm × 4.6 mm) with EtOAc/hexane (20:80) as eluent (Waters 486 absorbance detector, 254 nm). Carbohydrate numbering has been used for all compounds.

Allylation of Aldehyde 1

To a suspension of magnesium (0.44 g, 18 mmol) in anhyd Et_2O (5 mL) was added 3-bromobut-1-ene (1.85 mL, 13 mmol). The resulting solution was refluxed for 1 h and then cooled with an ice bath prior to the addition of the aldehyde **1** (1 g, 3.6 mmol) in Et_2O (2 mL). After further stirring for 1 h, the mixture was poured into sat. aq NH_4Cl and extracted with Et_2O. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. Flash column chromatography of the residue (silica gel, 10–15% EtOAc/petroleum ether) afforded **2** (*S*) as a white powder (0.78 g) and **3** (*R*) as an oil (0.18 g) in a 4:1 ratio. The overall yield was 80%.

6-*C*-Allyl-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (2)

Mp 90 °C, $[\alpha]_D^{20}$ –54.5 (*c* = 1.1, CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.33 and 1.49 (2 s, 6H, 2 CH_3), 1.56 (m, 2H, 2 H-6), 2.19 (m, 2H, 2 H-1'), 2.79 (s, 1H, OH), 3.96 (m, 3H, H-3, H-4, H-5), 4.48 (d, 1H, OC*H*Ph, *J* = 11.8 Hz), 4.67 (d, 1H, H-2, *J* = 3.8 Hz), 4.75 (d, 1H, OC*H*Ph, *J* = 11.8 Hz), 4.97 (m, 2H, 2 H-3'), 5.77 (m, 1H, H-2'), 5.97 (d, 1H, H-1, *J* = 3.8 Hz), 7.33 (m, 5H, 5 H arom).

^{13}C NMR ($CDCl_3$): δ = 26.5, 26.9, 29.7, 32.3, 69.4, 72.1, 82.6, 83.0, 105.0, 111.9, 114.8, 128.0, 128.3, 128.7, 138.4.

Anal ($C_{19}H_{26}O_5$): calcd C, 68.24; H, 7.84. Found C, 67.94; H, 7.61.

6-*C*-Allyl-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (3)

Oil,$[\alpha]_D^{20}$ –74 (*c* = 0.16, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.33 and 1.48 (2 s, 6H, 2 CH_3), 1.7 (m, 2H, 2 H-6), 2.17 (m, 2H, 2 H-1'), 3.93 (m, 1H, H-5), 3.97 (d, 1H, H-3, *J* = 2.8 Hz), 4.06 (t, 1H, H-4, *J* = 2.5 Hz), 4.45 (d, 1H, OCHPh, *J* = 11.8 Hz), 4.65 (d, 1H, H-2, *J* = 3.8 Hz), 4.75 (d, 1H, OCHPh, *J* = 11.8 Hz), 4.98 (m, 2H, 2 H-3'), 5.8 (m, 1H, H-2'), 5.97 (d, 1H, H-1, *J* = 3.8 Hz), 7.33 (m, 5H, 5 H arom).

Iodocyclization of Alcohols 2 and 3

A solution of the alcohol **2** or **3** (0.1 g, 0.23 mmol) in DMF (6 mL) was treated successively with $NaHCO_3$ (63 mg, 0.75 mmol) and I_2 (0.19 g, 0.75 mmol). After stirring at r.t. for 1 h, the mixture was quenched with H_2O and extracted with Et_2O. The organic layers were washed successively with sat. aq $Na_2S_2O_3$ and H_2O, dried (Na_2SO_4) and evaporated in vacuo. The residue was chromatographed (silica gel, 10–15% EtOAc/petroleum ether) to yield an inseparable mixture of *cis-trans* isomers **4**/**5** (72%) from alcohol **2** and *cis-trans* isomers **15**/**16** (58%) from alcohol **3**.

2',5-Anhydro-3-*O*-benzyl-6-deoxy-5-*C*-[(2'*R*,*S*)-2'-hydroxy-3'-iodopropyl]-1,2-*O*-isopropylidene-β-L-idofuranose 4/5

^{1}H NMR ($CDCl_3$): δ = 1.32 and 1.49 (2 s, 6H, 2 CH_3), 1.99 and 2.19 (2 m, 4H, 2 H-6, 2 H-1'), 3.17 (dd, 1H, H-3', *J* = 10 Hz), 3.33 (dd, 1H, H-3', *J* = 4 Hz), 3.88 (d, 1H, H-3, *J* = 3 Hz), 4.07 (t, 1H, H-4, *J* = 2.5 Hz), 4.13 (m, 1H, H-5), 4.37 (dd, 1H, H-2'), 4.45 (d, 1H, OCHPh, *J* = 12 Hz), 4.65 (d, 1H, H-2, *J* = 3.7 Hz), 4.71 (d, 1H, OCHPh, *J* = 12 Hz), 5.99 (d, 1H, H-1, *J* = 3.8 Hz), 7.33 (m, 5H, 5 H arom).

2',5-Anhydro-3-*O*-benzyl-6-deoxy-5-*C*-[(2'*R*,*S*)-2'-hydroxy-3'-iodopropyl]-1,2-O-isopropylidene-α-D-glucofuranose 15/16

^{1}H NMR ($CDCl_3$): δ = 1.3 and 1.4 (2 s, 6H, 2 CH_3), 1.76 and 2.2 (2 m, 4H, 2 H-6, 2 H-1'), 3.18 (dd, 1H, H-3', *J* = 10 Hz), 3.25 (dd, 1H, H-3', *J* = 4 Hz), 3.9 (d, 1H, H-3, *J* = 3 Hz), 4.01 (m, 1H, H-5), 4.1 (t, 1H, H-4, *J* = 2.3 Hz), 4.35 (dd, 1H, H-2'), 4.56 (d, 1H, H-2, *J* = 3.8 Hz), 4.68 (d, 2H, OCH_2Ph, *J* = 11.8 Hz), 5.9 (d, 1H, H-1, *J* = 4.1 Hz), 7.34 (m, 5H, 5 H arom).

Nucleophilic Displacement of Iodo Derivatives 4/5 and 15/16: Cesium Carbonate

To a solution of propionic acid (0.074 mL, 1 mmol) in DMF (0.15 mL) was added Cs_2CO_3 (0.33 g, 1 mmol). The mixture was stirred for 30 min before addition of **4**/**5** (52 mg, 0.11 mmol). The resulting solution was then heated at 60 °C overnight. Quenching with H_2O and extraction with Et_2O afforded a crude residue which was then separated by preparative layer chromatography (Merck silica gel 60 PF_{254}). An inseparable mixture of *cis-trans* esters **8a**/**9a** was obtained (25 mg, 56%) together with ketone **10** (15 mg, 41.5%).

The same procedure applied on the isomers **15**/**16** afforded an 58:42 ratio of esters **17**/**18** and ketone **19**, yield 90%.

2',5-Anhydro-3-*O*-benzyl-6-deoxy-5-*C*-[(2'*R*,*S*)-2'-hydroxy-3'-(propionyloxy)propyl]-1,2-*O*-isopropylidene-β-L-idofuranose 8a/9a

Oil; R_f 0.45 (EtOAc/petroleum ether 30:70).

IR (CH_2Cl_2): ν = 1026 and 1078 (C–O–C); 1462,2856, and 2928 (C–H); 1748 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.12 (t, 3H, $OCOCH_2CH_3$, *J* = 6 Hz), 1.32 and 1.5 (2 s, 6H, 2 CH_3), 1.68 and 1.97 (2 m, 4H, 2 H-6, 2 H-1'), 2.33 (q, 2H, $OCOCH_2$, *J* = 6 Hz), 3.89 (d, 1H, H-3, *J* = 2.8 Hz), 4.1 (m, 4H, H-4, H-5, 2 H-3'), 4.3 (m, 1H, H-2'), 4.45 (d, 1H, OC*H*Ph, *J* = 12 Hz), 4.65 (d, 1H, H-2, *J* = 4 Hz), 4.72 (d, 1H, OC*H*Ph, *J* = 12 Hz), 5.98 (d, 1H, H-1, *J* = 3.8 Hz), 7.33 (m, 5H, 5 H arom).

^{13}C NMR ($CDCl_3$): δ = 9.26 (C-12); 26.61 and 27.13 (2 CH_3); 27.50, 27.71, 28.19, 28.31, 28.56 (C-6, C-1', C-11); 66.42, 66.52, 71.97, 78.06, 78.14, 78.71, 82.28, 83.01, 83.16, 83.33, and 83.75 (C-2, C-3, C-4, C-5, C-2', C-3', OCH_2Ph); 105.81 (C-1); 111.88 (CMe_2); 127.92, 128.17, 128.68, and 137.62 (6 C arom); 174.43 (C-10).

HRMS (EI): *m/z* 406.1990 ($C_{22}H_{30}O_7$), calcd 406.1991.

2',5-Anhydro-3-*O*-benzyl-6-deoxy-5-*C*-[(2'*R*,*S*)-2'-hydroxy-3'-(propionyloxy)propyl]-1,2-*O*-isopropylidene-α-D-glucofuranose 17/18

Oil; R_f 0.4 (EtOAc/petroleum ether 15:85).

IR (CH_2Cl_2): ν = 1027, 1079, and 1215 (C–O); 1462, 2884, and 2941 (C–H); 1743 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 1.12 (t, 3H, $OCOCH_2CH_3$, *J* = 6 Hz), 1.3 and 1.48 (2 s, 6H, 2 CH_3), 1.73 and 2.02 (2 m, 4H, 2 H-6, 2 H-1'), 2.34 (q, 2H, $OCOCH_2$, *J* = 6 Hz), 4.01 (m, 5H, H-3, H-4, H-5, 2 H-3'), 4.28 (m, 1H, H-2'), 4.57 (d, 1H, H-2, *J* = 3.7 Hz), 4.66 (d, 2H, OCH_2Ph, *J* = 11.8 Hz), 5.99 (d, 1H, H-1, *J* = 3.8 Hz), 7.33 (m, 5H, 5 H arom).

^{13}C NMR ($CDCl_3$): δ = 8.96 (C-12); 26.17 and 26.76 (2 CH_3); 27.37 and 27.57 (C-11); 28.18, 28.87, and 29.39 (C-6, C-1'); 66.01, 66.25, 72.88, 75.73, 76.10, 77.79, 81.00, 82.62, 82.69, and 83.04 (C-2, C-3, C-4, C-5, C-2', C-3', OCH_2Ph); 105.13 (C-1); 111.43 and 111.48 (CMe_2); 127.50, 127.58, 128.24, 137.91, and 138.01 (6 C arom); 173.97 and 174.00 (C-10).

HRMS (EI): *m/z* 406.1990 ($C_{22}H_{30}O_7$), calcd 406.1991.

6-C-Acetonyl-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (10)
Mp 98 °C; $[\alpha]_D^{20}$ –72 (c = 0.07, $CHCl_3$); R_f 0.5 (EtOAc/petroleum ether 40:60).

IR (CH_2Cl_2): ν = 1025, 1077, and 1215 (C–O–C); 1455, 2871, and 2934 (C–H); 1719 (C=O); 3605 cm^{-1} (O–H).

^1H NMR ($CDCl_3$): δ = 1.33 and 1.48 (2 s, 6H, 2 CH_3), 1.72 (m, 2H, 2 H-6), 2.14 (s, 3H, 3 H-2'), 2.58 (m, 2H, 2 H-1'), 3.04 (s, 1H, OH), 3.98 (m, 3H, H-3, H-4, H-5), 4.45 (d, 1H, OC*H*Ph, *J* = 12 Hz), 4.65 (d, 1H, H-2, *J* = 3.8 Hz), 4.72 (d, 1H, OC*H*Ph, *J* = 12 Hz), 5.99 (d, 1H, H-1, *J* = 3.8 Hz), 7.33 (m, 5H, 5 H arom).

^{13}C NMR ($CDCl_3$): δ = 26.17 and 26.68 (2 CH_3); 26.90, 29.64, and 39.29 (C-6, C-1', C-3'); 68.71, 71.85, 72.97, 82.20, and 82.71 (C-2, C-3, C-4, C-5, OCH_2Ph); 104.74 (C-1); 111.63 (CMe_2); 127.73, 127.99, 128.42, and 136.78 (6 C arom); 208.37 (C-2').

HRMS (EI): *m/z* 350.1721 ($C_{19}H_{26}0_6$), calcd 350.1729.

Cesium Benzoate
Iodo compounds **4**/**5** (0.23g, 0.5 mmol) were dissolved in DMF (0.5 mL). Benzoic acid (20 mg, 0.17 mmol) and CsF (40 mg, 0.26 mmol) were successively added and the resulting solution was stirred at 60 °C overnight. The mixture was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. Chromatography (silica gel, 20–30% EtOAc/petroleum ether) afforded the benzoic esters **8b**/**9b** (72 mg, 32%) together with ketone **10** (54 mg, 30%).

2',5-Anhydro-3-*O*-benzyl-5-*C*-[(2'*R*,*S*)-3'-benzoyloxy-2'-hydroxypropyl]-6-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose 8b/9b
Oil; R_f 0.30 (EtOAc/petroleum ether 20:80).

IR (CH_2Cl_2): ν = 1025 and 1083 (C–O–C); 1452, 2873, and 2935 (C–H); 1725 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 1.33 and 1.5 (2 s, 6H, 2 CH_3), 1.83 and 2.05 (2 m, 4H, 2 H-6, 2 H-1'), 3.91 (d, 1H, H-3, *J* = 2.7Hz), 4.11 (t, 1H, H-4, *J* = 2.5 Hz), 4.38 (m, 4H, H-5, H-2', 2 H-3'), 4.46 (d, 1H, OC*H*Ph, *J* = 12 Hz), 4.65 (d, 1H, H-2, *J* = 3.7 Hz), 4.72 (d, 1H, OC*H*Ph, *J* = 12 Hz), 6 (d, 1H, H-1, *J* = 3.8 Hz), 7.31 (m, 10H, 10 H arom).

^{13}C NMR ($CDCl_3$): δ = 26.41 and 26.93 (2 CH_3); 27.39, 28.23, 28.48, and 29.69 (C-6, C-1'); 66.87, 71.79, 77.32, 78.04, 78.59, 82.1, 82.77, 82.98, 83.19, and 83.65 (C-2, C-3, C-4, C-5, C-2', C-3', OCH_2Ph); 105.63 (C-1); 111.76 (CMe_2); 127.73, 128.00, 128.32, 128.53, 129.74, 130.31, 132.89, and 137.39 (12 C arom); 166.55 (C=O).

HRMS (EI): *m/z* 454.1983 ($C_{26}H_{30}O_7$), calcd 454.1991.

Potassium Superoxide
To a solution of KO_2 (0.1 g, 1.5 mmol) and 18-crown-6 (40 mg, 0.15 mmol) in DMSO (3 mL) were added iodo compounds **4**/**5** (0.23 g, 0.5 mmol). After stirring for 30 min at r.t., the mixture was diluted with sat. aq brine and extracted with CH_2Cl_2. The combined organic layers were washed successively with sat. aq $Na_2S_2O_3$ and H_2O, dried (Na_2SO_4) and evaporated in vacuo. The crude product was chromatographed (silica gel, 10–30% EtOAc/petroleum ether) to yield **8c**/**9c** (0.1 g, 57%) and **10** (60 mg, 34%).

2',5-Anhydro-3-*O*-benzyl-6-deoxy-5-*C*-[(2'R,S)-2',3'-dihydroxypropyl]-1,2-*O*-isopropylidene-β-L-idofuranose 8c/9c
Oil; R_f 0.25 (EtOAc/petroleum ether 50:50).

IR (CH_2Cl_2): ν = 1028, 1078, and 1214 (C–O–C); 1454, 2873, and 2934 (C–H); 3495 cm^{-1} (O–H).

^1H NMR ($CDCl_3$): δ = 1.32 and 1.49 (2 s, 6H, 2 CH_3), 1.94 and 2.04 (2 m, 4H, 2 H-6, 2 H-1'), 2.41 (s, 1H, OH), 3.52 (dd, 1H, H-3', *J* = 11.8 and 5.9 Hz), 3.66 (dd, 1H, H-3', *J* = 11.8 and 3 Hz), 3.89 (d, 1H, H-3, *J* = 2.8 Hz), 4.09 (m, 2H, H-4, H-5), 4.27 (m, 1H, H-2'), 4.45 (d, 1H, OC*H*Ph, *J* = 12 Hz), 4.64 (d, 1H, H-2, *J* = 3.8 Hz), 4.71 (d, 1H, OC*H*Ph, *J* = 12 Hz), 5.98 (d, 1H, H-1, *J* = 3.7 Hz), 7.33 (m, 5H, 5 H arom).

^{13}C NMR ($CDCl_3$): δ = 14.04 (C-3'); 26.26 and 26.76 (2 CH_3); 27.30, 27.83, and 28.28 (C-6, C-1'); 60.13, 64.52, 71.66, 77.92, 79.59, 80.06, 81.9, 82.54, 83.33, and 83.48 (C-2, C-3, C-4, C-5, C-2', OCH_2Ph); 105.41 (C-1); 111.59 (CMe_2); 127.62, 127.85, 128.34, and 137.22 (6 C arom).

HRMS (EI): *m/z* 350.1732 ($C_{19}H_{26}O_6$), calcd 350.1729.

Tetrabutylammonium Nitrate
A mixture of **4**/**5** (46 mg, 0.1 mmol) and Bu_4NNO_3 (45.6 mg, 0.15 mmol) in benzene (1 mL) was heated and stirring for 7 d. The mixture was then poured into H_2O, extracted with Et_2O, dried (Na_2SO_4) and concentrated. The residue was purified by preparative layer chromatography (Merck silica gel 60 PF_{254}) to give **8d**/**9d** (22 mg, 56%) and **10** (10 mg, 29%).

2',5-Anhydro-3-*O*-benzyl-6-deoxy-5-*C*-[(2'*R*,*S*)-2'-hydroxy-3'-nitroxypropyl]-1,2-*O*-isopropylidene-β-L-idofuranose 8d/9d
Mp 72–74 °C; R_f 0.25 (EtOAc/petroleum ether 20:80).

IR (CH_2Cl_2): ν = 1027 and 1076 (C–O–C); 1452 and 2931 (C–H); 1641 cm^{-1} (O–NO_2).

^1H NMR ($CDCl_3$): δ = 1.32 and 1.49 (2 s, 6H, 2 CH_3), 1.74–2.04 (2 m, 4H, 2 H-6, 2 H-1'), 3.89 (d, 1H, H-3, *J* = 2.7 Hz), 4.08 (t, 1H, H-4, *J* = 2.5 Hz), 4.3 (m, 1H, H-2'), 4.45 (d, 1H, OC*H*Ph, *J* = 12 Hz), 4.47 (m, 3H, H-5, 2 H-3'), 4.66 (d, 1H, H-2, *J* = 3.8 Hz), 4.72 (d, 1H, OC*H*Ph, *J* = 12 Hz), 5.98 (d, 1H, H-1, *J* = 3.8 Hz), 7.34 (m, 5H, 5 H arom).

^{13}C NMR ($CDCl_3$): δ = 26.43 and 26.95 (2 CH_3); 27.30, 28.06, 28.58, 29.71 (C-6, C-1'); 71.84, 74.33, 74.42, 75.18, 75.51, 78.31, 78.85, 82.03, 82.12, 82.72, 82.94, and 83.28 (C-2, C-3, C-4, C-5, C-2', C-3', OCH_2Ph); 105.63 (C-1); 111.87 (CMe_2); 127.82, 128.09, 128.58, 137.32 (6 C arom).

HRMS (EI): *m/z* 395.1589 ($C_{19}H_{25}NO_8$), calcd 395.1580.

Debenzylation: General Procedure
To a solution of esters **8a**/**9a** (0.16 g, 0.39 mmol) in MeOH (0.8 mL) was added 10% Pd/C (32 mg). The resulting suspension was stirred for 1.5 h at r.t. under H_2. After filtration over Celite, MeOH was removed in vacuo. The residue was chromatographed (silica gel, 10–20% EtOAc/petroleum ether) to afford **11** and **12** in overall yield of 97% (120 mg).

The same procedure applied to **17**/**18** furnished **20** and **21** in a 70:30 ratio (95%).

2',5-Anhydro-6-deoxy-5-*C*-[(2'*S*)-2'-hydroxy-3'-(propionyloxy)propyl]-1,2-*O*-isopropylidene-β-L-idofuranose (11)
Mp 84–86 °C; $[\alpha]_D^{20}$ +8.5 (*c* = 0.12, $CHCl_3$); R_f 0.4 (EtOAc/petroleum ether 40:60).

IR (CH_2Cl_2): ν = 1017, 1076, and 1215 (C–O–C); 1463, 2882, and 2984 (C–H); 1744 (C=O); 3456 cm^{-1} (O–H).

^1H NMR ($CDCl_3$): δ = 1.13 (t, 3H, $OCOCH_2CH_3$, *J* = 6 Hz), 1.31 and 1.47 (2 s, 6H, 2 CH_3), 1.63 and 2.15 (2 m, 4H, 2 H-6, 2 H-1'), 2.36 (q, 2H, $OCOCH_2$, *J* = 6 Hz), 4.08 (m, 3H, H-4, 2 H-3'), 4.23 (d, 1H, H-3, *J* = 2.8 Hz), 4.36 (m, 1H, H-2'), 4.47 (m, 1H, H-5), 4.49 (d, 1H, H-2, *J* = 3.7 Hz), 4.6 (d, 1H, OH, *J* = 3.7 Hz), 5.95 (d, 1H, H-1, *J* = 3.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 9.01 (C-12); 26.14 and 26.83 (2 CH_3); 27.44 (C-11); 27.59 and 28.90 (C-6, C-1'); 65.89 (C-3'); 76.84 (C-3); 78.46, 78.48, and 85.54 (C-2, C-5, C-2'); 80.26 (C-4); 104.79 (C-1); 111.46 (CMe_2); 174.09 (C-10).

HRMS (EI): *m/z* 317.1607 ($C_{15}H_{24}O_7$), calcd for MH^+ 317.160028.

2',5-Anhydro-6-deoxy-5-*C*-[(2'*R*)-2'-hydroxy-3'-(propionyloxy)propyl]-1,2-*O*-isopropylidene-β-L-idofuranose (12)
Mp 44–46 °C; $[\alpha]_D^{20}$ –14 (*c* = 0.04, $CHCl_3$); R_f 0.3 (EtOAc/petroleum ether 40:60).

IR (CH_2Cl_2): ν = 1016, 1077, and 1215 (C–O–C); 1463, 2856, and 2929 (C–H); 1743 (C=O); 3460 cm^{-1} (O–H).

^{1}H NMR ($CDCl_3$): δ = 1.13 (t, 3H, $OCOCH_2CH_3$, *J* = 6 Hz), 1.32 and 1.48 (2 s, 6H, 2 CH_3), 1.91 and 2.12 (2 m, 4H, 2 H-6, 2 H-1'), 2.33 (q, 2H, $OCOCH_2$, *J* = 6 Hz), 4.05 (d, 2H, H-3'), 4.13 (d, 1H, H-3, *J* = 2.7 Hz), 4.25 (m, 2H, H-4, H-5), 4.48 (m, 2H, H-2, H-2'), 4.59 (d, 1H, OH, *J* = 3.7 Hz), 5.94 (d, 1H, H-1, *J* = 3.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 9.11 (C-12); 26.24 and 26.95 (2 CH_3); 27.41 (C-11); 27.55 and 29.07 (C-6, C-1'); 66.1 (C-3'); 76.4 and 78.66 (C-4, C-5); 79.17 and 85.67 (C-2, C-2'); 79.84 (C-3); 104.92 (C-1); 111.59 (CMe_2); 174.19 (C-10).

HRMS (EI): *m/z* 317.1600 ($C_{15}H_{24}O_7$), calcd for MH^+ 317.160028.

2',5-Anhydro-6-deoxy-5-*C*-[(2'*R*)-2'-hydroxy-3'-(propionyloxy)propyl]-1,2-*O*-isopropylidene-α-D-glucofuranose (20)
Oil; $[\alpha]_D^{20}$ –14 (*c* = 0.58, $CHCl_3$); R_f 0.25 (EtOAc/petroleum ether 30:70).

IR (CH_2Cl_2): ν = 1019 and 1076 (C–O–C); 1463, 2885, and 2983 (C–H); 1742 (C=O); 3516 cm^{-1} (O–H).

^{1}H NMR ($CDCl_3$): δ = 1.14 (t, 3H, $OCOCH_2CH_3$, *J* = 6 Hz), 1.31 and 1.48 (2 s, 6H, 2 CH_3), 1.75, 1.95, 2.08, 2.16 (4 m, 4H, 2 H-6, 2 H-1'), 2.34 (q, 2H, $OCOCH_2$, *J* = 6 Hz), 3.48 (s, 1H, OH), 4.07 (m, 3H, H-4, 2 H-3'), 4.28 (m, 3H, H-3, H-5, H-2'), 4.54 (d, 1H, H-2, *J* = 3.8 Hz), 5.96 (d, 1H, H-1, *J* = 3.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 9.04 (C-12); 26.17 and 26.83 (2 CH_3); 27.54, 27.79, 29.81 (C-6, C-1', C-11); 65.81 and 82.20 (C-4, C-3'); 75.33, 77.28, and 77.46 (C-3, C-5, C-2'); 85.25 (C-2); 105.23 (C-1); 111.51 (CMe_2); 174.51 (C-10).

HRMS (EI): *m/z* 316.1536 ($C_{15}H_{24}O_7$), calcd 316.1531.

2',5-Anhydro-6-deoxy-5-*C*-[(2'*S*)-2'-hydroxy-3'-(propionyloxy)propyl]-1,2-*O*-isopropylidene-α-D-glucofuranose (21)
Oil; $[\alpha]_D^{20}$ +16 (*c* = 0.09, $CHCl_3$); R_f 0.30 (EtOAc/petroleum ether 40:60).

IR (CH_2Cl_2): ν = 1018 and 1075 (C–O–C); 1463, 2884, and 2983 (C–H); 1744 (C=O); 3468 cm^{-1} (O–H).

^{1}H NMR ($CDCl_3$): δ = 1.14 (t, 3H, $OCOCH_2CH_3$, *J* = 6 Hz), 1.32 and 1.49 (2 s, 6H, 2 CH_3), 1.82, 1.95, 2.08, 2.16 (4 m, 4H, 2 H-6, 2 H-1'), 2.35 (q, 2H, $OCOCH_2$, *J* = 6 Hz), 3.41 (s, 1H, OH), 4.05 (m, 3H, H-3, 2 H-3'), 4.18 (m, 1H, H-5), 4.33 (m, 2H, H-4, H-2'), 4.54 (d, 1H, H-2, *J* = 3.7 Hz), 5.96 (d, 1H, H-1, *J* = 3.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 9.07 (C-12); 26.17 and 26.86 (2 CH_3); 27.28 and 29.10 (C-6, C-1'); 27.50 (C-11); 65.51 (C-5); 75.46 and 78.19 (C-4, C-2'); 77.52 and 81.93 (C-3, C-3'); 85.28 (C-2); 105.24 (C-1); 111.56 (CMe_2); 174.23 (C-10).

HRMS (EI): *m/z* 316.1530 ($C_{15}H_{24}O_7$), calcd 316.1531.

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