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Synthesis of a Tetrahydrofuran Fragment of Annonaceous Acetogenin from D-Galactal

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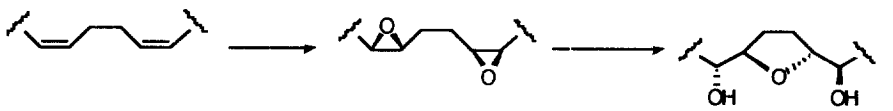
Abstract

Iodocyclisation of 6-*O*-pivaloyl-D-galactal followed by radical reduction at C-2 and S_N 2 conversion to a 3-*endo* iodide gave in good yield a [2.2.1] bicyclic acetal which can be regioselectively opened by *C*-nucleophiles (allyl silane or silyloxyfuran) in the presence of a Lewis acid to give 2,5-*trans*-disubstituted tetrahydrofurans.

Keywords: Acetogenins; Furans; Glycals; Silicon and compounds.

Various ionophore antibiotics [1] and a large group of the annonaceous acetogenins [2] are characterized by the presence of a tetrahydrofuran ring with two flanking hydroxyls which can be free or incorporated into other rings (tetrahydrofuran or tetrahydropyran). Biogenetic pathways explain (Scheme 1) relative and absolute configurations across the THF ring, annonacin type of acetogenin for instance being derived from a 1,5-*Z*,*Z* diene through a dehydrogenase-promoted *syn* bis-epoxidation followed by regioselective acid-base rearrangement:



1 *threo, trans, threo*

Scheme 1

Biological activities of annonaceous acetogenins have motivated many syntheses [3-5] where the main challenge remains the elaboration of a fragment such as **1** with four stereogenic centres encompassing the central THF ring and its flanking carbon atoms. Recent use of the "silyloxy diene methodology" [6] has allowed efficient syntheses [7-11] of these *C*-furanoside structures, the electrophilic module being obtained from L-glutamic acid or 2,3-*O*-isopropylidene-D-glyceraldehyde. A disconnective analysis (Scheme 2) shows however an obvious relationship of unit **1** to a D-galactofuranose unit. Our recent approach of furanosidic structures through iodocyclisation of pyranoid glycals [12] therefore suggests a possible route

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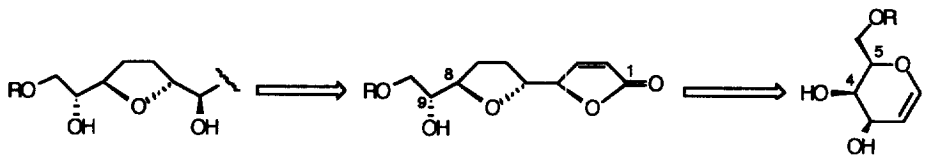
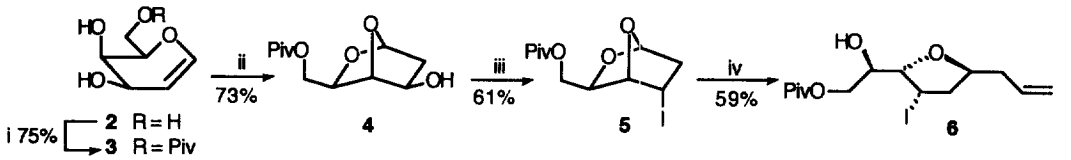
where stereogenic carbon atoms 8 and 9 of an intermediate butenolide would be related to the 4,5-*threo* configuration of D-galactose.



Scheme 2

Herein we report our preliminary results concerning the synthesis of fragment **1** from D-galactal **2**.

Regioselective pivaloylation at *O*–6 of D-galactal **2** with 3-pivaloyl-1,3-thiazolidine-2-thione (PTT) followed by *O*-tributylstannylation and *N*-iodosuccinimide (NIS)-promoted cyclisation, then radical reduction gave the [2.2.1] bicyclic acetal **4** (Scheme 3).



i. PTT, NaH, THF, 0°C; ii. $(Bu_3Sn)_2O$, 3Å mol. sieves, CH_3CN, reflux, then NIS, 0°C, then Bu_3SnH, AIBN, PhH, reflux; iii. Tf_2O, pyridine, CH_2Cl_2, -30°C, then $Bu_4N^+I^-$, DMF, 60°C; iv. $Me_3SiCH_2CH{=}CH_2$, Me_3SiOTf, EtCN, -78 → 0°C

Scheme 3

Attempted deoxygenation of a 3-*O*-phenoxythiocarbonate of **4** (Barton–Mc Combie conditions) failed, but a nucleophilic substitution of a 3-*O*-trifluoromethanesulfonate by iodide ions gave the crystalline *endo*-iodide **5** in 61% yield. The *endo* configuration of the iodine atom was confirmed by the high values of H-3 coupling constants $J_{2exo,3}$ (10.7 Hz) and $J_{3,4}$ (4.3 Hz) as compared to those of the *exo* compound **4** ($J_{2exo,3}$ = 1.5 and $J_{3,4}$ = 0 Hz). Irradiation of **5** with a tungsten lamp slowly released iodine, but no reduction product could be identified even in the presence of tributyltin hydride. Whether a radical was generated at C-3, it gives rise to intractable mixture of polar compounds in contrast with the behavior of the radical at C-2 [12].

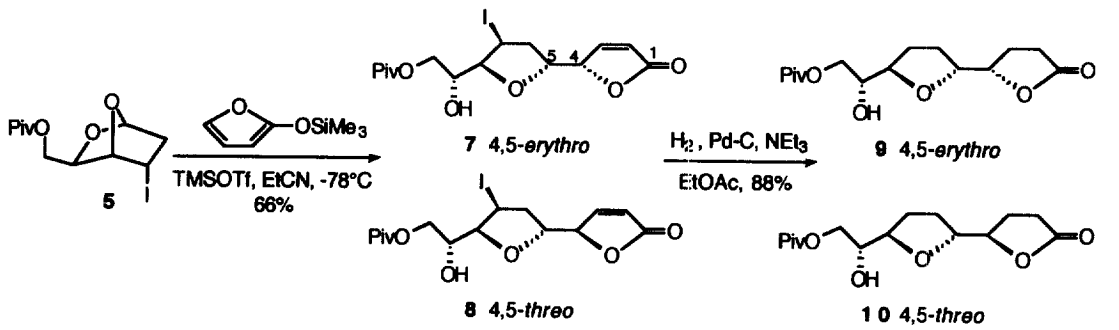
Synthesis of 1,4-anhydro-2,3-dideoxy-3-iodo-6-*O*-pivaloyl-β-D-*xylo*-hexopyranose 5: Trifluoromethanesulfonic anhydride (511 µL, 3.04 mmol) was added at -30°C to a solution of alcohol **4** (500 mg, 2.17 mmol) and pyridine (690 µL, 8.53 mmol) in dry CH_2Cl_2 (12 mL). The mixture was stirred at -30°C for 10 min, then diluted with CH_2Cl_2 (20 mL), washed with cold sat. aq. $NaHCO_3$ (10 mL) and water, dried ($MgSO_4$) and concentrated. Tetrabutylammonium iodide (2.4 g, 6.5 mmol) was added to a solution of the residue in DMF (10 mL) and the mixture was heated at 60°C under N_2, then cooled and diluted with ether (20 mL). The solution was washed with cold sat. aq. NaCl (20 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 95:5) to give **5** (450 mg, 61%), m.p. 56°C; $[\alpha]_D$ + 4 (*c* 0.99, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 5.42 (d, 1 H, $J_{1,2exo}$ 2.6 Hz, H-1), 4.52 (dd, 1 H, $J_{5,6a}$ 5.1, $J_{5,6b}$ 7.6 Hz, H-

5), 4.48 (d, 1 H, $J_{3,4}$ 4.3 Hz, H-4), 4.00 (dd, 1 H, $J_{5,6a}$ 5.1, $J_{6a,6b}$ 11.1 Hz, H-6a), 3.96 (ddd, 1 H, $J_{2endo,3}$ 5.3, $J_{2exo,3}$ 10.7, $J_{3,4}$ 4.3 Hz, H-3), 3.81 (dd, 1 H, $J_{5,6b}$ 7.6, $J_{6a,6b}$ 11.1 Hz, H-6b), 2.43 (ddd, 1 H, $J_{1,2exo}$ 2.6, $J_{2endo,2exo}$ 13.4, $J_{2exo,3}$ 10.7 Hz, H-2exo), 1.96 (dd, 1 H, $J_{2endo,2exo}$ 13.4, $J_{2endo,3}$ 5.3 Hz, H-2endo), 1.16 (s, 9 H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.99 (C=O), 101.28 (C-1), 80.61 and 75.76 (C-4,5), 63.59 (C-6), 44.47 (C-2), 38.78 (*C*Me_3), 27.19 (*CMe*$_3$), 16.46 (C-3). Calcd. for $C_{11}H_{17}IO_4$: C, 38.84; H, 5.04. Found: C, 39.07; H, 5.14.

Reactivity of the bicyclic acetal **5** with *C*-nucleophiles was first tested with allyltrimethylsilane. Addition in propionitrile at -78°C in the presence of trimethylsilyl trifluoromethanesulfonate gave the *C*-furanoside **6** (β:α 95:5) in 59% yield. Stereoelectronic control in the Lewis acid-promoted opening of the [2.2.1] bicyclic acetal gives a total regioselectivity; the good β-diastereoselectivity is explained either by a S_N2 reaction of the nucleophile [13] or by the steric hindrance of the iodine atom and the carbon chain at *C*-4 on the α-face of an intermediate oxycarbenium ion.

Addition of 2-(trimethylsilyloxy)furan to **5** in propionitrile in the presence of TMSOTf at -78°C then gave a 57:43 mixture of *erythro* **7** and *threo* **8** adducts in 66% yield (Scheme 4). The NMR signal of vinylic H-3 appears at lower field (δ 7.60) for the *erythro* compound than for the *threo* one (δ 7.48); Δδ 0.1-0.2 ppm are currently observed in 4-substituted butenolides [8,11,14,15]. Besides the *erythro* adduct has a larger $J_{4,5}$ value (5.6 Hz) than the *threo* one (3 Hz), the H-4–H-5 anti conformation being energetically more favorable for *erythro* configurations [11].

Hydrogenation of **7** and **8** in the presence of palladium and triethylamine gave a 1:1 mixture of *erythro* **9** and *threo* **10** bis-tetrahydrofurans in 88% yield.



Scheme 4

Addition of 2-(trimethylsilyloxy)furan to the [2.2.1] bicyclic acetal 5: Trimethylsilyl trifluoromethanesulfonate (107 μL, 0.59 mmol) was added to a solution of acetal **5** (200 mg, 0.59 mmol) and 2-(trimethylsilyloxy)furan (198 μL, 1.18 mmol) in dry propionitrile (5 mL) at -78°C under N_2. The mixture was stirred at -78°C for 210 min, then diluted with CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. Flash chromatography (ether) of the residue gave a 57:43 mixture of **7** and **8** (115 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) of **7**: δ 7.60 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 1.6 Hz, H-3), 6.23 (dd, 1 H, $J_{2,3}$ 5.8, $J_{2,4}$ 2.1 Hz, H-2), 5.17 (ddd, 1 H, $J_{2,4}$ 2.1, $J_{3,4}$ 1.6, $J_{4,5}$ 5.6 Hz, H-4), 4.51-4.38 (m, 2 H, H-5,7), 4.25-3.98 (m, 3 H, H-9,10a,10b), 3.48 (dd, 1 H, $J_{7,8}$ 4.1, $J_{8,9}$ 6.1 Hz, H-8), 2.90-2.40 (m, 2 H, H-6a,6b), 1.23 (s, 9 H, CMe_3);

^{1}H NMR (400 MHz, $CDCl_3$) of **8**: δ 7.48 (dd, 1 H, $J_{2,3}$ 5.8, $J_{3,4}$ 1.6 Hz, H-3), 6.21 (dd, 1 H, $J_{2,3}$ 5.8, $J_{2,4}$ 2.1 Hz, H-2), 5.11 (ddd, 1 H, $J_{2,4}$ 2.1, $J_{3,4}$ 1.6, $J_{4,5}$ 3 Hz, H-4), 4.63 (ddd, 1 H, $J_{4,5}$ 3, $J_{5,6a}$ 7.3, $J_{5,6b}$ 7.4 Hz, H-5), 4.51-4.38 (m, 1 H, H-7), 4.25-3.98 (m, 3 H, H-9,10a,10b), 3.41 (dd, 1 H, $J_{7,8}$ 4.3, $J_{8,9}$ 5.8 Hz, H-8), 2.90-2.40 (m, 2 H, H-6a,6b), 1.22 (s, 9 H, CMe_3).

A solution of **7** and **8** (325 mg, 0.77 mmol) and triethylamine (215 μL, 1.54 mmol) in EtOAc (10 mL) was hydrogenated at atmospheric pressure and room temperature for 12 h in the presence of 10% Pd-on charcoal (100 mg). The mixture was filtered over Celite and the catalyst was thoroughly washed with methanol. Combined filtrate and washings were concentrated and the residue was purified by flash chromatography (ether) to give a ~ 1:1 mixture of **9** and **10** (203 mg, 88%). ^{1}H (400 MHz, $CDCl_3$): δ 4.51-4.45, 4.18-4.08, 4.05-3.97 and 3.74-3.66 (4 m, 6 H, H-4,5,8,9,10a,10b), 2.70-1.66 (m, 8 H, H-2,3,6,7), 1.22 (2 s, 9 H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 178.67, 178.60, 177.48 and 177.14 (2 C=O), 81.56, 81.23, 81.18, 80.28, 80.20, 80.16, 71.76 and 71.52 (C-4,5,8,9), 65.79 and 65.77 (C-10), 38.82 (CMe_3), 28.19, 28.16, 27.97, 27.96, 27.91, 24.62 and 23.56 (C-2,3,6,7), 27.15 (CMe_3).

The lack of facial differentiation in the nucleophile may be attributed to a thermodynamic equilibrium between *erythro* and *threo* adducts [9]. But since the reaction occurs at very low temperature, it is more reasonable to postulate that electronic factors in such cyclic oxycarbenium species do not favor the Diels-Alder-like transition state leading usually to *threo* compounds [14,15]. To this respect *N*-Boc pyrrolidine electrophiles have been shown to strongly favor *threo* compounds [11]. Therefore it is possible that the use of other Lewis acids (especially chelating ones) might improve the diastereoselectivity by modifying the LUMO level of the electrophilic module.

In summary, we have shown that a core tetrahydrofuran fragment of various annonaceous acetogenins can be obtained in a limited number of steps from D-galactal. Extension to D-glucal would lead to *erythro, trans* configurations also found in the acetogenin family.

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