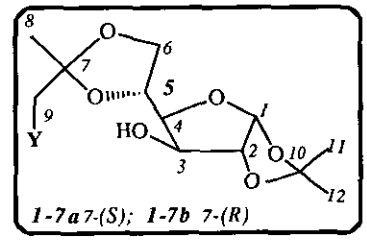
CHIRAL NUCLEOFUGALS: SYNTHESIS AND STRUCTURE OF FUNCTIONALISED ACETALS DERIVED FROM D-(+)-GLUCOSE

Pierre Duhamel*, Gerard Plé, and Jean-Yves Valnot

Université de Rouen, Faculté des Sciences, URA CNRS DO 464 et IRCOF
F-76821 Mont Saint Aignan, France

Abstract- D-(+)-Glucose derived iodoacetals (**1**) (Y= I) of known absolute configuration have been synthesized and their behaviour towards nucleophilic substitution was studied as a model for the synthesis of precursors of chiral nucleofugals with a pendant ligand.

The synthesis of chiral auxiliaries is a daily challenge for organic chemists. Our continuing interest for the enantioselective alkylation of enolates[1] led us to design new alkylating reagents with chiral nucleofugals[2] such as mixed sulfates derived from D-(+)-glucose. From a structure-stereoselectivity relationship study, a model has been previously proposed highlighting the role of the oxygen atom linked to the carbon 5 of the glucose moiety *via* its coordination with the lithium atom of the enolate in an intramolecular process.[3] Then, we became interested in the possibility of a second coordinating site **Y** (Y= OR, SR, NRR'...) to held the reagents rigidly in space in an appropriate relative orientation for the alkylation to take place;[4] this internal solvatation might result in a kinetic rate enhancement and hopefully a better stereochemical control. According to molecular models, only two carbon atoms are necessary between the two coordinating sites and finally these alcohols have to be synthesized on gramm scale with known and predictable absolute configuration of the new chiral center.



1-7a 7-(S); 1-7b 7-(R)

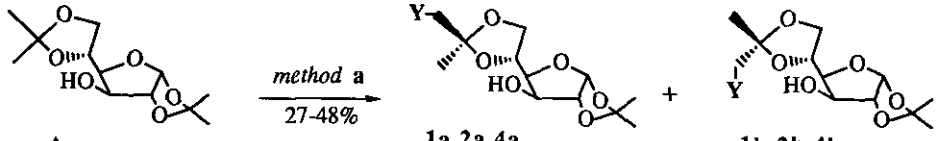
In this paper, we wish to report on the synthesis of alcohols (**1-7**) (Y= OR, SR, N_3).

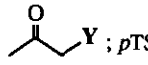
Mixed acetals **(2a,b)** (Y= OMe) and **(4a,b)** (Y= SPh) have been obtained when commercial 1,2;5,6-bis-*O*-(1-methylethylidene)-α-(D)-glucofuranose **(A)** was subjected to acid catalysed transacetalization with the corresponding ketone. We found that yields and purity could be greatly improved by conducting the reaction under ultrasonic conditions in benzene at 45 °C (method **a**, Table 1). However, yields remained moderate and this approach was limited by three observations:

-the yield of the reaction is dramatically affected by the crowding of the parent ketone.

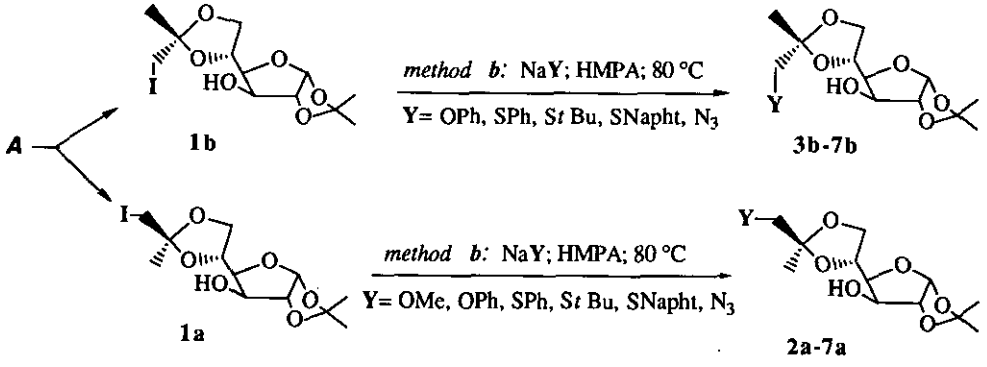
-when the separation is possible, iterative chromatography is required for a complete separation of each epimer of the new stereogenic center and this is at the origin of a significant loss of material.

-the necessity for determining the structure of each epimer in each case.



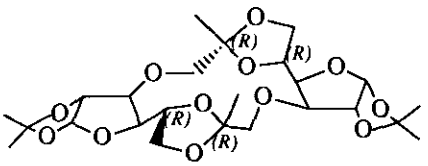
method **a**:  ; *p*TSA/benzene, 45 °C;))) ; **Y**= I, OMe, SPh.

Finally these difficulties have been partially overcome when we found that the transacetalization with 1-iodo-propan-2-one, in the same conditions,[5] gave the corresponding iodoacetal in 48% yield as a thermodynamic 3/7 mixture of two epimers **(1a)** and **(1b)**.[6] Fortunately, it was possible to partially separate the two epimers by crystallization and to epimerise them under acidic conditions (*p*TSA, benzene, 45 °C).



These iodoacetals (**1a,b**) proved to be suitable precursors for the corresponding thioethers and amino-precursors since the nucleophilic substitution of the neopentyl iodide took place in good yields (78-92%) with sodium thiolates and azide using HMPA as the solvent[7] (method **b**, Table 1).

On the contrary, the result of the substitution with alkoxides was dependent on the configuration of the iodoacetal and the basicity of the alkoxide. Ether (**2a**) (Y= OMe) obtained in a moderate yield (30%) by substitution of epimer (**1a**) with 1.5 to 5 equivalents of sodium methoxide in HMPA at 80 °C is identical with a sample[8] prepared by method **a**. With epimer (**1b**), in the same conditions, only the product (**D**) of self condensation was obtained with 62% yield. Similar results have been obtained using sodium phenate as the base: **3a** was obtained from **1a** with 65% yield; on the other hand, **1b** gave a mixture of **3b** (32%) and (**D**) (25%). It can be assumed that the formation of the corresponding alkoxide strongly mediates the reactivity of the iodine atom, this allosteric effect did not take place with epimer (**1a**), substitution being faster. The macrocycle (**D**) has been simply synthesized by reacting one equivalent of base (NaH, *t*BuOK, *t*BuONa, *t*BuOLi) in the usual conditions.[9]



D

All these compounds have been fully characterized by ^{1}H and ^{13}C nmr spectroscopy. The proton assignment required 1D proton coupled spectra, COSY $^{1}H/^{1}H$ homonuclear correlated spectra and Nuclear Overhauser Effect difference spectroscopy (NOE). The absolute configuration of the new stereogenic center of iodo-compounds (**1a**) and (**1b**) could be ascertained using NOE difference experiments; these results allowed for the attribution of the absolute configuration of compounds (**2-7**) and were confirmed by the NOE of **2a,b** .[10] The ^{13}C chemical shifts have been attributed on the basis of the ^{1}H nmr spectra in conjunction with the two dimensional heteronuclear $^{1}H/^{13}C$ correlation technic. From all the data collected, it has to be noticed that only the ^{13}C chemical shifts of the new acetalic group gave an homogeneous sequence: for all compounds, the chemical shift of the methyl group is displaced upfield for the (*S*)-epimers (**1-7a**) compared with the (*R*)-epimers (**1-7b**) while the opposite sequence is observed for the methylene group of CH_2Y (see Table 1).

$\delta_{(CH_3)}$ **(1-7 a)** > $\delta_{(CH_3)}$ **(1-7 b)** $\quad\quad$ $\delta_{(CH_2Y)}$ **(1-7 a)** < $\delta_{(CH_2Y)}$ **(1-7 b)**

Table 1 Synthesis of alcohols **(1-7)**. Yields and ^{13}C chemical shifts

Y	Structure	Yield % (*)		^{13}C nmr δ ppm; C_6D_6	
		(a)	(b)	CH_3	CH_2Y
I	**1a** (*S*)	15		24.67	12.02
	1b (*R*)	33		23.22	12.64
OMe	**2a** (*S*)	25	30	23.36	76.49
	2b (*R*)	8	**	22.34	77.45
OPh	**3a** (*S*)		65	23.03	71.29
	3b (*R*)		32***	22.10	71.54
SPh	**4a** (*S*)	12	82	25.42	43.07
	4b (*R*)	15	85	24.35	43.84
2-SNapht	**5a** (*S*)		85	25.50	43.07
	5b (*R*)		80	24.42	43.73
S*t* Bu	**6a** (*S*)		92	25.60	37.50
	6b (*R*)		85	24.63	38.63
N_3	**7a** (*S*)		78	23.26	55.63
	7b (*R*)		92	22.30	58.42

* method (a): transacetalization then flash chromatography; method (b): nucleophilic substitution from **1**.

** 62% self condensation product **D**. *** **3b** is accompanied by 25% of **D**.

Glucose acetals are potential auxiliaries for enantio- and diastereoselective reactions.[11] The methodology developed here proved to be useful for the synthesis of acetals derived from D-(+)-glucose with a pendant nucleophilic ligand.

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5. A procedure for transacetalization; benzene solution (150 ml) of the glucose acetonide (13 g, 50 mmol) was sonicated 20 min at 45 °C with 0.3 g of *p*TSA; to the gel thus obtained was added 1-iodopropan-2-one (13.8 g, 75 mmol) and the mixture was sonicated again 5 h. Then the solution was washed successively with 2x40 ml of concentrated $NaHCO_3$, 30 ml of water and concentrated under vacuo. The residue was taken up with 150 ml of dry benzene, 1-iodopropan-2-one (1.8 g, 10 mmol), 0.2 g *p*TSA and sonicated 5 h again. In those conditions the transformation is nearing completion. The mixture of acetals was separated from the excess of iodopropanone by filtration over silica gel. **1b** was partially crystallized and the remaining mixture was separated by flash chromatography[12] (Petroleum ether/AcOEt 65/35).
6. Compound **1a**; R_f= 0.32 (AcOEt/ Pet. Eth. 35/65); $[\alpha]_D$ -1.4° (c= 2.32, $CHCl_3$, 27 °C); mp 116 °C (Et_2O/ n-hexane); ir υ max (nujol): 3460; ms m/z (EI): 371 (M^+-15), 245. Anal. Calcd for $C_{12}H_{19}O_6I$: C, 37.32; H, 4.96. Found: C, 36.97; H, 4.84. ^{1}HNmr (400 MHz, C_6D_6) δ 1.05 (s, 3H^{11}), 1.36 (s, 3H^8), 1.40 (s, 3H^{12}), 1.60 (d, J=4.3 Hz, OH), 2.91 (AB, J=11 Hz, 2H^9), 3.91 (d, J=6.2 Hz, 2H^6), 4.10 (dd, J=4.3, 2.9 Hz, 1H^3), 4.17 (d, J=3.5 Hz, 1H^2), 4.22 (dd, J=7.4, 2.9 Hz, 1H^4), 4.35 (dt, J=7.4, 6.2 Hz, 1H^5), 5.81 (d, J=3.5 Hz, 1H^1). ^{13}CNmr (100 MHz, C_6D_6) δ 12.02 (C^9), 24.67 (C^8), 26.71 (C^{11}), 27.52 (C^{12}), 68.72 (C^6), 74.97 (C^2), 75.57 (C^4), 82.06 (C^3), 86.08 (C^5), 106.2 (C^1), 108.42 (C^7), 112.27 (C^{10}).

   Compound **1b**; R_f= 0.26 (AcOEt/ Pet. Eth. 35/65); $[\alpha]_D$ -7.5° (c= 2.77, $CHCl_3$, 28 °C); mp 164 °C (Et_2O/ n-hexane); ir υ max (nujol): 3460; ms m/z (EI): 371 (M^+-15), 245. Anal. Calcd for $C_{12}H_{19}O_6I$: C, 37.32; H, 4.96. Found: C, 37.05; H, 4.80. ^{1}HNmr (400 MHz, C_6D_6) δ 1.07 (s, 3H^{11}), 1.24 (s, 3H^8), 1.42 (s, 3H^{12}), 2.98 (d, J=11 Hz, 1H^9), 3.02 (d, J=11 Hz, 1H$^{9'}$), 3.88 (dd, J=8.4, 6.3 Hz,

$1H^6$), 4.00 (dd, J=8.5, 6.1 Hz, $1H^{6'}$), 4.16 (d, J=3.6 Hz, $1H^2$), 4.24 (dd, J=4.1, 2.9 Hz, $1H^3$), 4.28 (dt, J=7.8, 6.3 Hz, $1H^5$), 4.40 (dd, J=7.8, 2.9 Hz, $1H^4$), 5.80 (d, J=3.6 Hz, $1H^1$). ^{13}C Nmr (100 MHz, C_6D_6) δ 12.64 (C^9), 23.22 (C^8), 26.77 (C^{11}), 27.62 (C^{12}), 69.13 (C^6), 74.53 (C^2), 75.77 (C^4), 82.17 (C^3), 86.17 (C^5) 106.24 (C^1), 110.84 (C^7), 112.22 (C^{10}).

7. A procedure for the nucleophilic substitution; the thiol (1.6 mmol) was reacted in 2 ml THF with NaH (0.045 g, 1.1 mmol. 60% in oil) under argon then the iodoacetal **1a** or **1b** (0.39 g, 1 mmol) in 4 ml dry HMPA was added and the mixture heated 8 h at 85 °C. Ether (70 ml) was added and the solution was washed successively with water (10 ml) and 20% ammonium chloride (10 ml). Evaporation of the solvent gave a solid which was purified by filtration over silicagel and recrystallized.

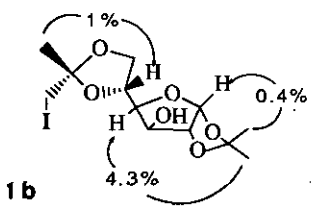
8. Compound **2a**; oil; R_f= 0.27 (AcOEt/ Pet. Eth. 44/56); $[\alpha]_D$ -2.1° (c= 2.9, $CHCl_3$, 28 °C); (Et_2O/ n-hexane); ir υ max (nujol): 3460; ms m/z (CI, *i*But): 291 (M^++1), 245. Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.63. Found: C, 54.02; H, 7.86. ^1HNmr (400 MHz, C_6D_6) δ 1.08 (s, $3H^{11}$), 1.39 (s, 3H), 1.40 (s, 3H), 3.08 (s, 3H), 3.13 (d, J=10.3 Hz, $1H^9$), 3.17 (d, J=10.3 Hz, $1H^{9'}$), 3.29 (s, OH), 4.06 (dd, J=5.6, 8.2 Hz, $1H^6$), 4.13 (dd, J=6.1, 8.3 Hz, $1H^{6'}$), 4.31 (dd, J=2.8, 8.2 Hz, $1H^4$), 4.40 (m, $1H^3$), 4.42 (d, J=3.6 Hz, $1H^2$), 4.54 (dt, J=5.9, 8.3 Hz, $1H^5$), 5.81 (d, J=3.6 Hz, $1H^1$). ^{13}C Nmr (100 MHz, C_6D_6) δ 23.36 (C^8), 26.71 (C^{11}), 27.50 (C^{12}), 59.73, 69.02 (C^6), 74.21 (C^2), 75.27 (C^3), 76.49 (C^9), 82.67 (C^4), 86.25 (C^5), 106.23 (C^1), 109.85 (C^7), 112.21 (C^{10}).

Compound **2b**; R_f= 0.31 (AcOEt/ Pet. Eth. 44/56); $[\alpha]_D$ -1.4° (c= 1.93, $CHCl_3$, 28 °C); mp 78 °C; ir υ max (nujol): 3460; ms m/z (CI, *i*But): 291 (M^++1), 245. Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.63. Found: C, 53.92; H, 7.46. ^1HNmr (400 MHz, C_6D_6) δ 1.06 (s, $3H^{11}$), 1.26 (s, $3H^8$), 1.42 (s, $3H^{12}$), 2.79 (s, OH), 3.09 (s, 3H), 3.17 (d, J=10.3 Hz, $1H^9$), 3.22 (d, J=10.3 Hz, $1H^{9'}$), 3.91 (dd, J=6.2, 8.3 Hz, $1H^6$), 3.97 (dd, J=7.2, 8.3 Hz, $1H^{6'}$), 4.28 (dd, J=2.8, 6.9 Hz, $1H^4$), 4.31 (m, $1H^3$), 4.34 (d, J=3.6 Hz, $1H^2$), 4.41 (dt, J=7.3, 6.3 Hz, $1H^5$), 5.93 (d, J=3.6 Hz, $1H^1$). ^{13}C Nmr (100 MHz, C_6D_6) δ 22.34 (C^8), 26.74 (C^{11}), 27.53 (C^{12}), 59.70, 68.66 (C^6), 74.15 (C^2), 75.48 (C^3), 77.45 (C^9), 81.97 (C^4), 86.38 (C^5), 106.16 (C^1), 110.16 (C^7) 112.15 (C^{10}).

9. A procedure for the dimerization of **1b**; HMPA (4 ml) solution of **1b** (0.39 g, 1 mmol) was added to a suspension of NaH (0.04 g, 1 mmol, 60% in oil) in 1 ml THF. After 1 h at room temperature the mixture was heated at 85 °C during 8 h. Final treatment and purification[7] gave the dimer with 89% yield.

Dimer **D**; $[\alpha]_D$ -40.3° (c= 1.83, $CHCl_3$, 27 °C); mp 102 °C (Et_2O/ n-hexane); ms m/z (CI, NH_3): 535, 477, 276(100), 243. Anal. Calcd for $C_{24}H_{36}O_{12}$: C, 55.80; H, 7.02. Found: C, 55.72; H, 7.22. ^1H Nmr (200 MHz, C_6D_6) δ 1.06 (s, 3H), 1.09 (s, 3H), 1.43 (s, 3H), 3.08 (dd, J=8.1, 0.8 Hz, $1H^6$), 3.23 (dd, J=8.1, 8.0 Hz, $1H^{6'}$), 3.41 (d, J=12.2 Hz, $1H^9$), 3.55 (d, J=12.1 Hz, $1H^{9'}$), 3.87 (br t, J=1.7 Hz, $1H^3$), 4.09 (br d, J=1.6 Hz, $1H^4$), 4.40 (d, J=3.6 Hz, $1H^2$), 4.43 (br d, J=6.6 Hz, $1H^5$), 6.00 (d, J=3.8 Hz, $1H^1$). ^{13}C Nmr(50 MHz, C_6D_6) δ 23.23, 26.02, 26.94, 65.81, 75.63, 77.00, 81.10, 81.73, 84.88, 104.90, 109.44, 111.29.

10. NOE difference experiments clearly substantiate the absolute configuration postulated for **1a,b** and **2a,b**



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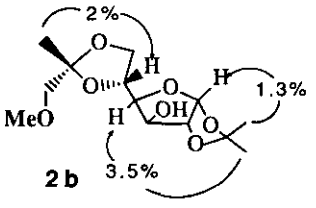

2 b

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