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Design and Reactivity of Organic Functional Groups - Preparation and Nucleophilic Displacement Reactions of Imidazole-1-sulfonates (Imidazylates)

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Key words: S_N2 displacement, imidazole-1- sulfonate group

Abstract: Imidazole-1-sulfonate, a new type of leaving group by remote activation, allows facile S_N2 substitution reactions at sterically crowded centers with various nucleophiles under mild conditions. It could be easily prepared from alcohols with cheap reagents in quantitative yield.

Functional group manipulation involving leaving groups[1] is an operational necessity in the daily practice of organic chemistry. The great variety of functional groups acting as nucleofugal groups, coupled with the large differences in rates of reactions of nucleophiles[2] allows selective conversions of alcohols to other groups. Sulfonate esters are the most frequently used leaving groups because of their good nucleofugal properties, their ease of preparation, and their favorable rates of reactions. Sulfonic esters serve as intermediates in numerous synthetic transformations.[3] Moreover, reactions of sulfonate esters have played an important role in the development of many fundamental concepts on which modern chemistry is based such as reaction mechanisms, neighboring group participation, non-classical carbocations, solvent effects on reactivity, and linear free-energy relationships.[4] The introduction of perfluoroalkane sulfonic esters, particularly triflates,[5] has considerably extended the range of reactivity of sulfonic esters, and added a new dimension to S_N2 displacement reactions. Some triflate esters have a limited shelf-life and they may be somewhat impractical for large scale synthesis because of the price of reagents. For these and other reasons, there have been many efforts to develop new leaving groups.

We describe herein details of our studies on the preparation and reactivity of imidazole-1-sulfonates (imidazylate or Imz).[6] The design of this leaving group was predicated upon a number of features that are

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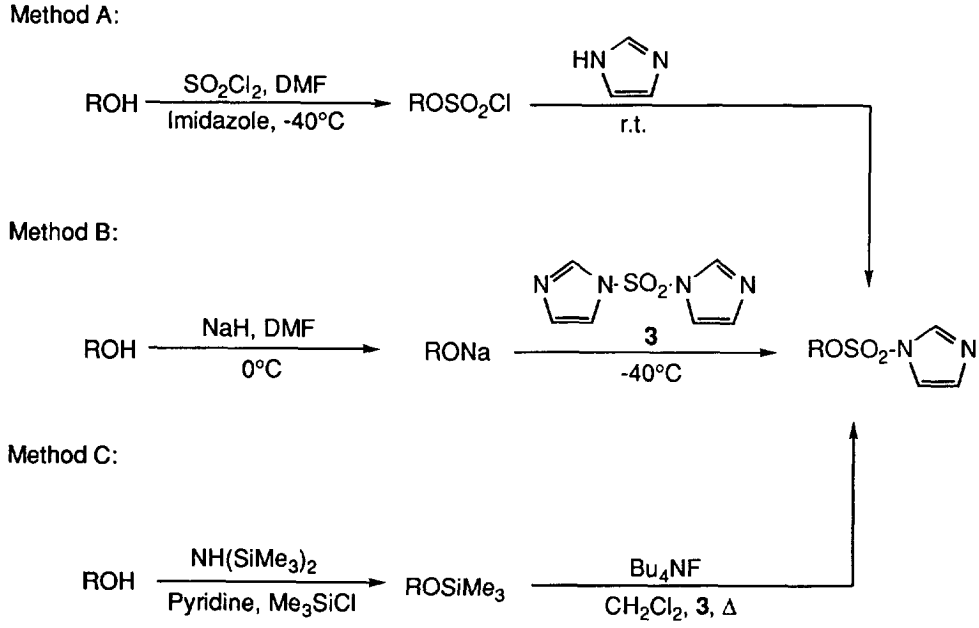
inherent in its structure. Thus, we expected greater reactivity than an alkyl or arylsulfonate because of the presence of an electron withdrawing heterocycle, and the fact that the N-imidazole-1-sulfonate group might fragment to imidazole and SO_3 once released in solution. The added option of remote activation[7] by transforming the heterocycle into an imidazolium salt during the reaction would enhance its nucleofugal properties even greater.

In order to determine the nucleofugal properties of imidazole-1-sulfonates in bimolecular substitution reactions, we chose alcohols from the carbohydrate field. The corresponding tosylates have been known to undergo S_N2 displacement reactions with difficulty.[8]

RESULTS AND DISCUSSION

Synthesis of imidazole-1-sulfonates from alcohols

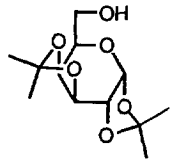
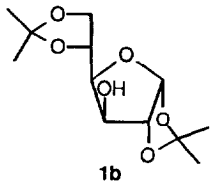
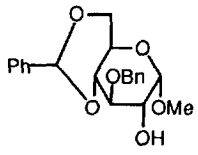
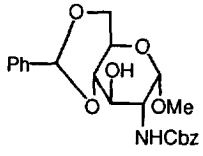
Imidazylates can be prepared in three different ways (Scheme I). In Method A, reaction of alcohols with sulfuryl chloride in DMF at -40°C in the presence of 6 equiv. of imidazole, gives a chlorosulfate ester[9] as an intermediate. The chlorine atom is then substituted by imidazole at room temperature to afford imidazylates in good yields (Table 1, entries 1,3,6,8, 81-96%). Method B consists in the treatment of the sodium alcoholates, generated *in situ* (NaH, DMF) with an excess of N',N-sulfuryldiimidazole[10] (1.5 equiv.) at -40°C to give the corresponding imidazylates (Table 1, entries 2, 4, 7, 85-91% yield). In Method C, the tetrabutylammonium alkoxide generated from its corresponding trimethylsilyl ether by Bu_4NF is allowed to react with N,N'-sulfuryldiimidazole to give the imidazylate in high yield (Table 1, entry 5).



Scheme I.

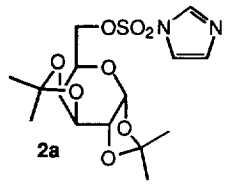
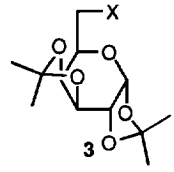
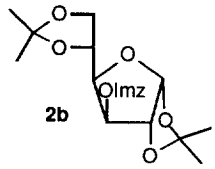
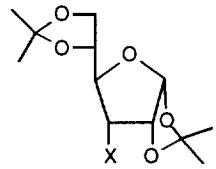
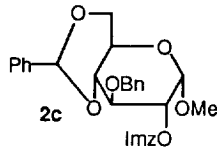
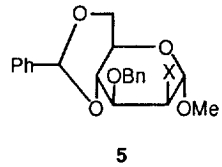
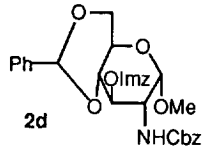
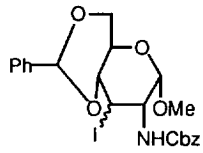
The imidazylate esters shown in Table 1 are stable crystalline solids or syrups, with an excellent shelf life.

Table 1. Preparation of imidazylates from alcohols.

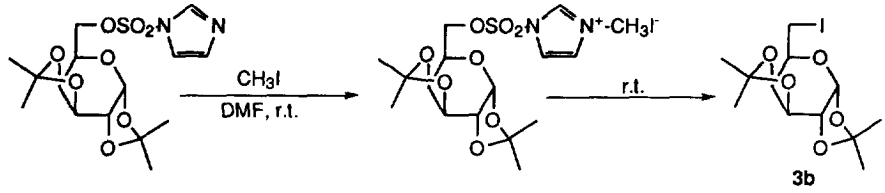
Entry	Substrate	Method	% Isolated yield of imidazylate	
1	 1a	A	2a	81
2		B		85
3	 1b	A	2b	91
4		B		85
5		C		91
6	 1c	A	2c	96
7		B		91
8	 1d	A	2d	87

It is known that displacement of 6-alkyl- and arylsulfonates of D-galactopyranose derivatives with charged nucleophiles necessitates high temperatures and long reaction times because of considerable steric overcrowding in the transition state, and of unfavorable dipolar interactions between the C-4-O-4 dipole and the charged nucleophile. In contrast, using the imidazylate as leaving group (compound **2a**), the substitution takes place at room temperature with azide and halide ions, including fluoride, (Table 2, entries 1,2,4).[6] Treatment of a primary imidazylate with methyl iodide in the presence of an acid scavenger (imidazole) affords the iodide[11a] **2a** in 78% yield, (Scheme II, Table 2, entry 3). These reactions have been extended to a disaccharide derivative. [12]

Table 2 . Reactivity of imidazylates with nucleophiles

Entry	Substrate/Nucleophile[a]	Product	Temp, °C	Time, h	% Yield
	 **2a**	 **3**			
1	Bu_4NF	**a** X=F	25	3	75
2	Bu_4NI	**b** X=I	25	6	81
3	MeI	X=I	25	8	78
4	Bu_4NN_3	**c** $X=N_3$	25	6	81
	 **2b**	 **4**			
5	NaI/DMF	**a** X=I	100	10	48
6	Bu_4NI	X=I	80	72	72
7	Bu_4NN_3	**b** $X=N_3$	80	5	62
	 **2c**	 **5**			
8	Bu_4NCl	**a** X=Cl	110	6	78
9	Bu_4NI	**b** X=I	110	6	92
10	Bu_4NN_3	**c** $X=N_3$	110	6	90
11	Bu_4NOBz	**d** X=OBz	110	4	85
	 **2d**	 **6**			
12	Bu_4NI		80	3	90

a. Reactions were done in toluene unless otherwise stated.



Scheme II.

When the nucleophilic substitution is reasonably facile (primary alcohols, non-sterically hindered secondary alcohols), Method A (SO_2Cl_2, imidazole, DMF) gives exclusively the chloride derivative. This can be explained by the fact that the chlorosulfate ester intermediate is a very good leaving group,[9] and the substitution at the carbon site by chloride ions is faster than the substitution of chlorine by imidazole at the sulfur site (Scheme 1).

The tosylate of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose is particularly reluctant to undergo nucleophilic substitution with charged nucleophiles because of dipolar interactions[13] and significant proportions of the elimination product are always formed. Although substitution by bromide and iodide ions was made possible by the use of triflate esters[14] and oxyphosphonium salts,[15] elimination was still observed.

Displacement of the 3-imidazylate of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **2b** by azide and iodide ions occurs readily in toluene to give mainly the substitution products **4a**, and **4b** (72% and 62% yield respectively, Table 2, entries 6,7) along with the elimination product (29% and 12% yield respectively). As seen in Entry 5, the yield of **4a** is lower in dipolar solvents, in favor of the formation of the elimination product. The structures of compounds **4a** and **4b** were confirmed by ^1H NMR spectroscopy and by comparison of their optical rotations with those described in the literature.[15,16] David and Alais[17] reported an S_N2 displacement reaction on **2b** with tetrabutylammonium benzoate in 68% yield.

Displacement of 2-O-tosylate esters of methyl α-D-glucopyranoside derivatives does not normally occur, and the absence of reactivity has been rationalized in terms of torsional strain and electrostatic and steric interactions in the transition state.[18] There are only a few examples in the literature of substitution at the C-2 position of alkyl α-D glucopyranoside derivatives with charged nucleophiles.[19] As seen in Table 2 (Entries 8-11), displacement of the corresponding 2-imidazylate of the glucopyranoside derivative **2c** occurs readily with various nucleophiles and in very good yields. Displacement with benzoate and azide anions are particularly noteworthy. Reduction of the 2-halo derivatives **5a** and **5b** with tributyltin hydride gave the corresponding known 2-deoxy analog.[20] Paulsen and coworkers[21] used a 2-imidazylate and nitrate ion in the synthesis of a disaccharide. Hashimoto and coworkers[22] successfully displaced a 2-imidazylate with azide ion in the synthesis of benzyl 2-azido-2-deoxy-3,4-O-isopropylidene-β–D-hexopyranoside. Imidazylate esters have also been used to transform D-galacto derivatives into the corresponding D-gluco derivatives in a disaccharide with tetrabutylammonium benzoate at room temperature.[23]

Normally difficult displacement reactions in furanose derivatives have been rendered feasible by using a 2-imidazylate in the presence of fluoride or azide ions on a 1 mole scale in excellent yields.[24] David and co-

workers have successfully displaced a 2-imidazylate ester in a D-glucofuranoside derivative with azide ion in 82% yield.[25]

Next, we turned our attention to the nucleophilic substitution at C-3 of a 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside derivative (Table 2, entry 12). This displacement is sluggish because of the steric hindrance of the axial anomeric substituent[13] and an oxazolidone can be obtained[26] instead of the expected substitution product by participation of the N-carbamate.

Nucleophilic substitution of the 3-imidazylate **2d** by iodide ions was effected in toluene (80°C, 3h) and provided the corresponding iodide (presumed to be an epimeric mixture at C-3) in 90% yield.[27] This product was efficiently reduced by tributyltin hydride in refluxing toluene, in the presence of AiBN, to furnish the corresponding 3-deoxy derivative[28] in 90% yield. Displacement of an axial imidazylate in a D-altroside derivative with tetrabutylammonium acetate in refluxing toluene gave the corresponding methyl 3-O-acetyl-2-azido-2-deoxy-4,6-O-benzylidene-α-D-mannopyranoside in 63% yield.[29] Vicinal imidazylates have been utilized in the synthesis of 2,3-unsaturated sugar derivatives by treatment with Zn powder and sodium iodide.[30]

Imidazylates have found utility outside the carbohydrate area such as in the formation of monobactams by intramolecular azetidinone formation.[31]

In conclusion, we have shown that imidazylate esters are excellent leaving groups which can be displaced by various nucleophiles. The imidazylate group has several advantages over other well-established nucleofugal groups in the organic chemistry. Unlike some triflates, imidazylates have excellent shelf lifes, and they can be prepared from cheap reagents. The method also complements and competes with the Mitsunobu reaction[15,32] where the removal of the redox by-products Ph_3PO and diethoxycarbonylhydrazine, can be laborious and problematic on large scale.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured on a Perkin-Elmer polarimeter model 141 at 22-24°C. The ^1H and ^{13}C spectra were recorded on a Bruker WH90 instrument with tetramethylsilane as internal standard in deuteriochloroform as solvent. IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Unicam SP100 spectrophotometer. Sulfuryl chloride was distilled before use. Benzene, dichloromethane, dimethylformamide, pyridine and toluene were distilled from calcium hydride.

General procedure for the preparation of imidazole-1-sulfonates from alcohols.

Method A

To a solution of alcohol (1 mmol) and imidazole (0.41g; 6 mmol) in 5 mL of DMF, cooled to -40°C, was added under nitrogen, sulfuryl chloride (0.12 mL, 1.5 equiv.). The solution was stirred for 1 h at room temperature, water was added, followed by ether or dichloromethane depending of the solubility of the sulfonate. The aqueous phase was extracted once with ether or dichloromethane, the combined organic extracts were washed twice with water, dried (Na_2SO_4) and evaporated.

1,2:3,4-Di-O-isopropylidene-6-O-(N-imidazole-1-sulfonyl)-D-galactopyranose , (**2a**).
The residue obtained from 0.8 g of **1a** was purified by chromatography on silica gel (ether-petroleum ether, 2:1) to give 0.975g (82% yield) of **2a** obtained as an oil; $[\alpha]_D$ -55° (c, 1.16, CH_2Cl_2). IR (neat): 3100, 3070, 1630 cm^{-1} (imidazole ring); ^1H NMR: δ 7.91 (s, H-2'), 7.36 (s, H-5'), 7.16 (s, H-4'), 5.43 (d, 1H, H-1, J = 5.6Hz), 4.61 (q, 1H, H-3, J = 3.8Hz), 1.51, 1.36, 1.32, 1.29 (4s, 12H); Anal. calcd. for $C_{15}H_{22}N_2O_8S$: C, 46.15; H, 5.68; N, 7.16; S, 8.21. Found 45.94; H, 5.53; N, 6.95; S, 8.13.

1,2:5,6-Di-O-isopropylidene-3-O-(N-imidazole-1-sulfonyl)-D-glucofuranose , (**2b**).

The residue obtained from 1g of **1b** was purified by chromatography on silica gel (ether-petroleum ether, 2:1) to furnish 1.36 g (91% yield) of a crystalline imidazylate **2b**, mp 98-99°C (ether-hexane); $[\alpha]_D$ -76.3° (c, 0.8, CH_2Cl_2). IR (KBr): 3100, 3070, 1610 cm^{-1} (imidazole ring); ^1H NMR: δ 7.98 (s, H-2'), 7.37 (s, H-5'), 7.15 (s, H-4'), 5.96 (d, 1H, H-1, J = 3.9Hz), 4.9 (s, 1H, H-3), 4.75 (d, 1H, H-2), 4.2 (m, 4H), 1.50, 1.32, 1.26, 1.22 (4s, 12H). Anal. calcd. for $C_{15}H_{22}N_2O_8S$: C, 46.15; H, 5.68; N, 7.16; S, 8.21. Found: C, 45.95; H, 5.61; N, 7.14; S, 8.27.

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-(N-imidazole-1-sulfonyl)-α-D-glucopyranoside, (**2c**).

Chromatography of the residue obtained from 1g of **1c**[33] (ether-petroleum ether, 3:1) gave 1.3 g of **2c** as an oil (96%); $[\alpha]_D$ +29.2° (c, 0.59, CH_2Cl_2). ^1H NMR: δ 7.92 (s, H-2'), 5.52 (s, 1H, PhC*H*), 4.75, d, 1H, H-1, J = 4Hz), 4.67 (q, 2H, O*CH*$_2$Ph, J = 11Hz), 3.37 (s, 3H, OMe). Anal. calcd. for $C_{24}H_{26}N_2O_8S$: C, 57.36; H, 5.21; S, 6.38. Found: C, 57.10; H, 5.40; S, 6.18.

Methyl 4,6-O-benzylidene-2-benzyloxycarbonylamino-2-deoxy-3-O-(N-imidazole-1-sulfonyl)-α-D-glucopyranoside, (**2d**).

The residue obtained from 1 g of compound **1d**[34] was chromatographed on silica gel (chloroform-ethylacetate, 4:1) gave 1.14 g of the crystalline imidazylate **2d** (87%), mp 128-129° (ethyl acetate); $[\alpha]_D$ + 18.2° (c, 0.33, CH_2Cl_2). ^1H NMR: δ 7.92 (s, 1H, H-2'), 7.01 (s, 1H, H-4'), 5.52 (s, 1H, PhC*H*), 4.75 (d, 1H, H-1, J = 3Hz), 4.65 (q, 2H, O*CH*$_2$Ph), 3.37 (s, 3H, OMe). Anal. calcd. for $C_{25}H_{27}N_3O_9S$: C, 55.03; H, 4.98; N, 7.70; S, 5.87. Found C, 54.92; H, 4.91; N, 7.68; S, 5.84.

Method B

To an ice-chilled solution of alcohol (1 mmol) in 5 mL of DMF, was added under nitrogen sodium hydride (60% dispersion in mineral oil, 0.06 g; 1.5 equiv.), the suspension was stirred at room temperature for 30 min and cooled to -40°C. N,N'-Sulfuryldiimidazole[10] (0.298 g, 1.5 equiv.) in 3 mL of DMF was added and stirred for 30 min at -40°C. MeOH (0.2 mL) was added and the stirring was continued for 30 min at -40°C. The DMF solution was added in cold water and extracted twice with ether. The combined ethereal extracts was washed with water until pH 7, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by chromatography on silica gel. 1,2:3,4-Di-O-isopropylidene-6-O-(N-imidazole-1-sulfonyl)-α-D-galactopyranose **2a** was obtained in 85% yield; $[\alpha]_D$ + 54.2° (c, 0.5, CH_2Cl_2); 1,2:5,6-Di-O-isopropylidene-3-O-(N-imidazole-1-sulfonyl)-α-D-glucofuranose **2b**, mp 99-99.5°C; $[\alpha]_D$ - 76.1° (c, 0.9 CH_2Cl_2) in 85% yield; methyl 3-O-benzyl-4,6-O-

benzylidene-2-O-(N-imidazole-1-sulfonyl)-α-D-glucopyranoside **2c** in 81% yield; $[\alpha]_D$ +28.7° (c, 0.42, CH_2Cl_2).

Method C

1,2:5,6-Di-O-isopropylidene-3-O-(N-imidazole-1-sulfonyl)-α-D-glucofuranose, **(2b).**

To a solution of 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **1b** (0.4 g, 1.5 mmol) in 5 mL of pyridine were successively added 1 mL of hexamethyldisilazane and 0.5 mL of chlorotrimethylsilane. The solution was stirred for 30 min at room temperature and evaporated to dryness. The residue was dissolved in 10 mL of dichloromethane and 2.5 mL of tetrabutylammonium fluoride in THF (1M), N,N'-sulfuryldiimidazole (0.46 g, 1.5 equiv.) were successively added. The solution was refluxed, under nitrogen for 4h, diluted with dichloromethane, washed twice with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (ether-petroleum ether, 2:1) to give the crystalline imidazylate **2b** (91%), identical in all respects with an authentic sample.

6-Deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose, **(3a).**

To a solution of **2a** (166 mg, 0.426 mmol) in toluene (6 mL) was added tetrabutylammonium fluoride (1.11 mL of 1M solution) and the solution was stirred at room temperature for 3h. The solution was diluted with toluene (20 mL), washed with water, and the organic extracts were processed in the usual manner to give a syrup. Purification by silica gel chromatography (ether-petroleum ether, 1:4) gave 76 mg (68%) of the expected fluoride **3a**, as a syrup; $[\alpha]_D$ -53.2° (c, 1.5, $CHCl_3$); reported[35], $[\alpha]_D$ -51.4° (c, 1.28, $CHCl_3$).

6-Deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose, **(3b).**

To a solution of imidazylate **2a** (0.25 g, 0.6 mmol) in 2.5 mL of DMF was added 0.24 g (2.5 equiv.) of sodium iodide. The solution was stirred for 6h at room temperature, diluted with ether, washed with a saturated solution of sodium thiosulfate and water. The ethereal extracts were dried on Na_2SO_4, and evaporated. The oily residue was purified on a pad of silica gel (ether-petroleum ether, 1:4) to give 0.191 g of an oil (81%) which crystallized slowly on standing, mp 70°C; $[\alpha]_D$ -47.3° (c, 0.82, CH_2Cl_2); reported[11a] mp 70°C; $[\alpha]_D$ -50°.

To a solution of imidazylate **2a** (0.25 g, 0.6 mmol) were added imidazole (0.04 g, 0.9 equiv.) and iodomethane (0.5 mL, 12 equiv.). The solution was stirred for 8h and processed as described above. The title compound **3b** was obtained in 78% yield; $[\alpha]_D$ -48° (c, 1.2, CH_2Cl_2).

6-Azido-6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose, **(3c).**

To a solution of compound **2a** (0.3 g, mmol) in 3 mL of DMF was added sodium azide (0.1 g, 3 equiv.) and the solution was stirred for 6 h at room temperature. Water and ether were added, and the organic layer was washed several times with water, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on silica gel (ether-petroleum ether, 1:4) to afford 0.17 g of an oil (81%); $[\alpha]_D$ -90.5° (c, 0.86, CH_2Cl_2); reported[11b] $[\alpha]_D$ -92.1° (c, 1.48, $CHCl_3$).

3-Deoxy-3-iodo-1,2:5,6-di-O-isopropylidene-α-D-allofuranose, **(4a).**

To a solution of imidazylate **2b** (0.4 g, 1 mmol) in 6 mL of DMF were added sodium iodide (0.65 g, 10 mmol) and imidazole (0.08 g, 1 mmol). The solution was heated at 100°C, under nitrogen for 10h, then allowed to cool to room temperature. A saturated solution of sodium thiosulfate and ether were added, the ethereal layer was washed several times with water, dried (Na_2SO_4) and evaporated. The residue, purified by chromatography on silica gel (ether-petroleum ether, 1:3) gave first the elimination product (0.072 g, 8%); mp 51°C. The second fraction consisted of the iodo derivative **4a** (0.182g, 48%) obtained as an oil; $[\alpha]_D$ +67.2° (c, 0.52, CH_2Cl_2); reported[15] $[\alpha]_D$ +64°. ^1H NMR: δ 5.82 (d, 1H, H-1, J = 3.9 Hz), 4.62 (t, 1H, H-2, J = 4 Hz), 3.81 (q, 1H, H-3, J = 9Hz).

To a solution of compound **2b** (0.2 g, 0.5 mmol) in 5 mL of benzene was added tetrabutylammonium iodide (0.55 g, 3 equiv.). After refluxing the solution for 72 h, ether was added followed by a saturated solution of sodium thiosulfate. The organic layer was washed once with water, dried (Na_2SO_4) and evaporated. Chromatography on silica gel of the residue (ether-petroleum ether, 1:3) gave first 3-deoxy-1,2:5,6-di-O-isopropylidene-D-*erythro*-hex-3-enofuranose (0.018 g, 12%), followed by the iodo derivative **4a** (0.133 g, 72%).[15]

3-Azido-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose, **(4b).**

To the solution of the imidazylate **2b** (0.3g, 0.8 mmol) in 9 mL of toluene were added sodium azide (0.15 g, 3 equiv.) and tetrabutylammonium chloride (0.64 g, 3 equiv.).[36] The suspension was stirred for 30 min at room temperature and 5h at 80°C. The toluene solution was washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed to give the unsaturated by-product sugar first (0.055g, 29%), then the 3-azido derivative **4b** (0.136g, 62%) as an oil; $[\alpha]_D$ +74.6° (c, 1.90, CH_2Cl_2); reported[15,16] $[\alpha]_D$ +72° (c, 1, $CHCl_3$). ^1H NMR: δ 5.78 (d, 1H, H-1, J = 3.9 Hz), 4.74 (t, 1H, H-2, J = 4 Hz), 3.52 (q, 1H, H-3, J = 8.5 Hz), 1.58, 1.48, 1.38 (3s, 12 H).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-chloro-2-deoxy-α-D-mannopyranoside, **(5a).**

To a solution of compound **2c** (0.3 g, 0.6 mmol) in 8 mL of toluene was added tetrabutylammonium chloride (0.5 g, 3 equiv.). The solution was refluxed for 6h, diluted with toluene, washed twice with water, dried (Na_2SO_4) and evaporated. Chromatography on silica gel (ether-petroleum ether, 1:3) gave the chlorosugar **5a** (0.18 g, 78%) as an oil; $[\alpha]_D$ +3.1° (c, 0.29, CH_2Cl_2). ^1H NMR: δ 5.61 (s, 1H, PhC*H*), 4.85 (d, 1H, H-1, J = 1.7 Hz), 4.74 (s, 2H, Ph-CH_2), 3.35 (s, 3H, OMe).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-2-iodo-α-D-mannopyranoside, **(5b).**

To a solution of the imidazylate **2c** (0.5 g, 1 mmol) in 10 mL of toluene was added tetrabutylammonium iodide 1,1 g, 3 equiv.). The solution was refluxed 16 h, diluted with toluene, washed with a saturated solution of sodium thiosulfate then water. The organic extracts were dried (Na_2SO_4) and evaporated to dryness. Purification on silica gel (ether-petroleum-ether, 1:4) gave the iodo derivative **5b** (0.39 g, 82%) as an oil; $[\alpha]_D$ -34.2° (c, 0.5, CH_2Cl_2); ^1H NMR: δ 5.62, (s, 1H, PhC*H*), 5.11, (s, 1H, H-1), 4.71 (s, 2H, PhCH_2), 3.35 (s, 3H, OMe).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-deoxy-α-D-arabino-hexopyranoside

Compound **5b** (0.3 g, 0.6 mmol) was dissolved in 20 mL of toluene and tributyltin hydride (0.4 mL, 2 equiv.) and azobisisobutyronitrile (0.02 g) were added. The solution was heated at 80°C for 15 min under nitrogen. TLC (ether-petroleum ether, 1:3) of the reaction mixture showed the formation of the 2-deoxy sugar. After evaporation of the solvent, the residue was chromatographed on silica gel (ether-petroleum ether, 1:3) to give the crystalline 2-deoxy derivative (0.16 g, 73%), mp 101-102° (hexane);$[\alpha]_D$ +64.9° (c, 0.26, CH_2Cl_2); reported[20], mp 105.5°-106°C; $[\alpha]_D$ + 73.8° (c 0.8, $CHCl_3$). Reduction of the 2-chloro **5a** gave identical results

Methyl 2-azido-3-O-benzyl-4,6-di-O-benzylidene-2-deoxy-α-D-mannopyranoside, **(5c).**

To a solution of the imidazylate **2c** (0.55 g, 1.1 mmol) in 10 mL of toluene were added tetrabutylammonium chloride (0.91 g, 3 equiv.) and sodium azide (0,25 g, 3.5 equiv.). After stirring at room temperature for 30 min, the solution was refluxed for 6 h, washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (ether-petroleum ether, 1:3) to furnish the 2-azido derivative **5c** (0.39 g, 90%) as an oil; $[\alpha]_D$ + 30.1 (c, 5.4, CH_2Cl_2). IR (neat): N_3, 2100 cm^{-1}; ^1H NMR: δ 5.62 (s, 1H, PhC*H*), 4.8 (s, 2H, PhCH_2), 4.66 (d, 1H, H-1, J = 1.9 Hz), 3.34 (s, 3H, OMe).

Methyl 3-O-benzyl-4,6-O-benzylidene-2-O-benzoyl-α-D-mannopyranoside, **(5d).**

A solution containing the imidazylate **2c** (0.25 g, 0.5 mmol) and tetrabutylammonium benzoate (0.78 g, 2 mmol) in 8 mL of toluene was heated at 100°C for 4h. The solution was diluted with toluene, washed twice with water, dried (Na_2SO_4) and evaporated. The residue, chromatographed on silica gel (ether-petroleum ether, 1:4), gave compound **5d** (0.20 g, 85%) as a foam; $[\alpha]_D$ -56.7°; $[\alpha]_{436}$ -130.5° (c, 0.37, CH_2Cl_2); reported[37] $[\alpha]_D$ -52.9° and $[\alpha]_{436}$ -123° (c, 1, $CHCl_3$). IR (KBr): carbonyl 1730 cm^{-1}; ^1H NMR: δ 8.1 (m, 2H), 5.68 (s, 1H, PhC*H*), 5.58 (m, 1H, H-2), 4.82 (d, 1H, H-1, J = 1.6 Hz), 4.71 (2H, PhCH_2), 3.39 (s, 3H, OMe).

Methyl 4,6-O-benzylidene-2-benzyloxycarbonylamino-2,3-dideoxy-3-iodo-α-D-allo and D- glucopyranoside, **(6).**

A solution containing the imidazylate **2d** (0.4 g, 0.74 mmol) and tetrabutylammonium iodide (0.84 g, 3 equiv.) in 8 mL of benzene was refluxed for 3 h. The solution was diluted with chloroform, washed with a saturated solution of sodium thiosulfate, water, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel (ethyl acetate-chloroform, 2:98) afforded **6** (0.345 g, 90%) as a foam which crystallized slowly in ethanol, mp 110-111°C. The configuration at C-3 of the product was not determined.

Methyl 4,6-O-benzylidene-2-benzyloxycarbonylamino-2,3-dideoxy-α-D-ribo-hexopyranoside.

To a solution of the 3-iodosugar **6** (0.5 g, 0.9 mmol) in 5 mL of toluene were added under nitrogen, azobisisobutyronitrile (0.02 g) and tributyltin hydride (0.3 mL, 1.2 equiv.). The solution was heated for 30 min at 80°C, then evaporated to dryness. After trituration of the residue with petroleum ether, the precipitate was filtered and purified by chromatography on silica gel (chloroform-ethyl acetate, 98:2) to give the crystalline 3-deoxy amino sugar (0.305 g, 84%); mp 175-176° (chloroform-ether); $[\alpha]_D$ + 50.9° (c, 0.33, CH_2Cl_2); ^{13}C NMR: δ 155.3 (C=O), 137.3, 136.1, 128.9, 128.4, 128.1, 126.1 (C aromatic), 101.5 (PhCH), 97.9 (C-

1), 76.3 (C-4), 69.1 (C-6), 66.8 (Ph-CH_2), 63.8 (C-5), 54.9 (OCH_3), 49.3 (C-2), 31.0 (C-3). Anal. calcd. for $C_{22}H_{25}NO_6$: C 66.15, H 6.3, N 3.51; found C 65.71, H 6.29, N 3.54.

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