Synthesis of Chiral Ionic Liquids from Natural Monosaccharides

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In memory of our friend and colleague Prof. Cinzia Chiappe (Università di Pisa, Italy)

Three series of new ionic liquids (ILs), namely imidazolium-, pyrazolium-, and bis-benzimidazolium-containing ILs, were prepared from low-cost, unprotected carbohydrates. Informa-tion on anion-cation interactions and solvation shell were obtained via diffusion NMR and heteronuclear Overhauser correlation maps (HOESY), respectively.

Introduction

Ionic liquids[1] (ILs) are special molten salts with melting points below 100 °C typically constituted of organic cations (e.g. imidazolium, pyridinium, pyrrolidinium, triazolium ions) and inorganic or organic anions (e.g. halide, triflate, dicyanamide ions) (Figure 1). Thanks to their ionic nature, they feature non-measurable vapor pressure, low or no flammability and good solvent properties for a wide range of inorganic, organic and polymeric materials. Therefore, in order to develop more environmentally compatible syntheses, ILs may replace the traditional organic solvents. However, most of these alternative solvents are prepared starting from fossil feedstock while only a limited number of ILs were synthesized from renewable sources[1c] (e.g. hydroxy acids, amino acids, terpenes). As reviewed by us[2] and others,[3] some ionic liquids were also obtained from carbohydrates,[4] the most important class of
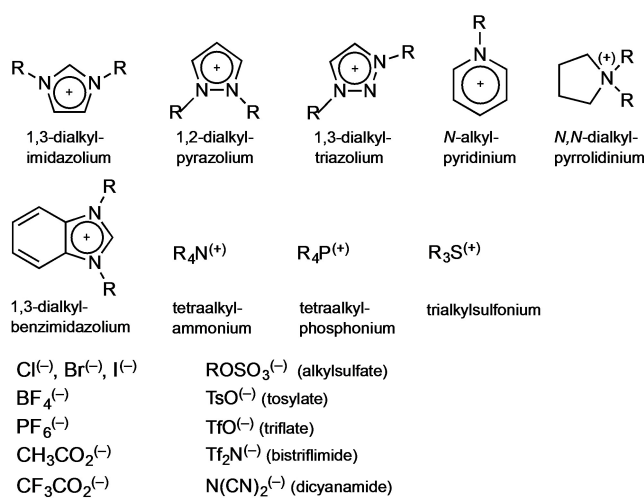

Figure 1. Structure of cations and anions commonly found in ionic liquids.

renewable raw material, very often by reaction of suitably functionalized cyclic or acyclic sugars with *N*-heterocycles.

We describe here the synthesis and physicochemical characterization of new imidazolium-, pyrazolium-, and bis-benzimidazolium ionic liquids from various low-cost monosac-charidic sugars, including the L-sorbose (**5**, see Scheme 1). The latter, although belonging to the less common L-series, is a readily available and inexpensive monosaccharide widely used for the industrial large-scale synthesis of the L-ascorbic acid (vitamin C). It is worth pointing out that, contrary to the majority of the already known[2–4] sugar-based ILs, these new ILs were prepared starting from nitrogenated heterocycles that are obtained directly from unprotected carbohydrates instead of covalently linking a preformed heterocycle to a suitably functionalized sugar. Interestingly, the choice of the starting natural pentose or hexose allows the synthesis of both achiral (e.g. **30**, Scheme 3, and **47**, Scheme 4) and enantiopure ionic liquids (e.g. **16**, Scheme 1, **34**, Scheme 3, and **56**, Scheme 5).

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EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202200100

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Results and Discussion

The imidazolium-based ionic liquids **16–20** (Scheme 1) were obtained from the corresponding 4-polyhydroxyalkyl-imidazole derivatives **6–10**, in turn prepared[5] by reaction of the inexpensive monosaccharides **1–5** with formamidine acetate.

However, the reported[5] synthesis of **7–10** was carried out by heating at 75 °C for 15 h (in a stainless-steel autoclave, ca. 40 bar) a mixture of sugar and formamidine acetate in the presence of liquid ammonia as the solvent. After initial attempts, we decided to explore less drastic reaction conditions, in particular by avoiding the use of liquid ammonia and conventional heating. The best results were observed when a suspension of the pentoses **1–2** or hexoses **3–5** (10 mmol, 1.5–1.8 g) and formamidine acetate (1.2 equiv.) in DMF was heated at 120 °C for 30 min under MW irradiation (single-mode cavity Biotage Initiator oven). The reaction mixtures were then adsorbed on an acid ion exchange resin, washed with water and desorbed with 10% aqueous ammonia to give the crude imidazole derivatives that were purified by column chromatography on silica gel. Unfortunately, the known[5] compounds **8–10** were isolated together with small amounts of unidentified by-products, therefore they were submitted to the following step and isolated as *O*- and *N*-alkylated products **13–15**. In order to tune the hydrophilic properties of the target ionic liquids, the alkylation of the polyols **6–10** was performed with methyl iodide and *n*-octyl bromide in the presence of sodium hydride. However, in the former case, besides the hydroxyl groups, both the nitrogen atoms were methylated to directly afford the corresponding ionic liquids which could not be purified. On the other hand, the alkylation with 1-bromooctane and NaH allowed to isolate the octylated products **11–15** in a pure form after column chromatography. Treatment of a DMF solution of the latter with an excess of methyl iodide gave, after 1 h at 50 °C, the ionic liquids **16–20** in high yield.

Alberto Marra graduated in Pharmaceutical Sciences from the University of Pisa (Italy) and obtained his PhD degree from the University of Paris VI (France) under the supervision of Prof. P. Sinaÿ (Ecole Normale Supérieure). After a post-doctoral fellowship at the University of Zurich (Switzerland) with Prof. A. Vasella, he joined the group of Prof. A. Dondoni at the University of Ferrara (Italy). In 1998 he became Professor in Organic Chemistry and in 2012 he moved to the University of Montpellier (France) where he joined the Institute of Biomolecules Max Mousseron (IBMM). Since 2015, he has been leading the Glycochemistry and Molecular Recognition team at IBMM. He is Editor-in-Chief of Letters in Organic Chemistry (Bentham Science) since 2018. Recent work is dealing with the synthesis of multivalent sugars and iminosugars through metal-free ligations such as the thiol-ene coupling (TEC), thiol-yne coupling (TYC) and sulfur(VI) fluoride exchange (SuFEx).
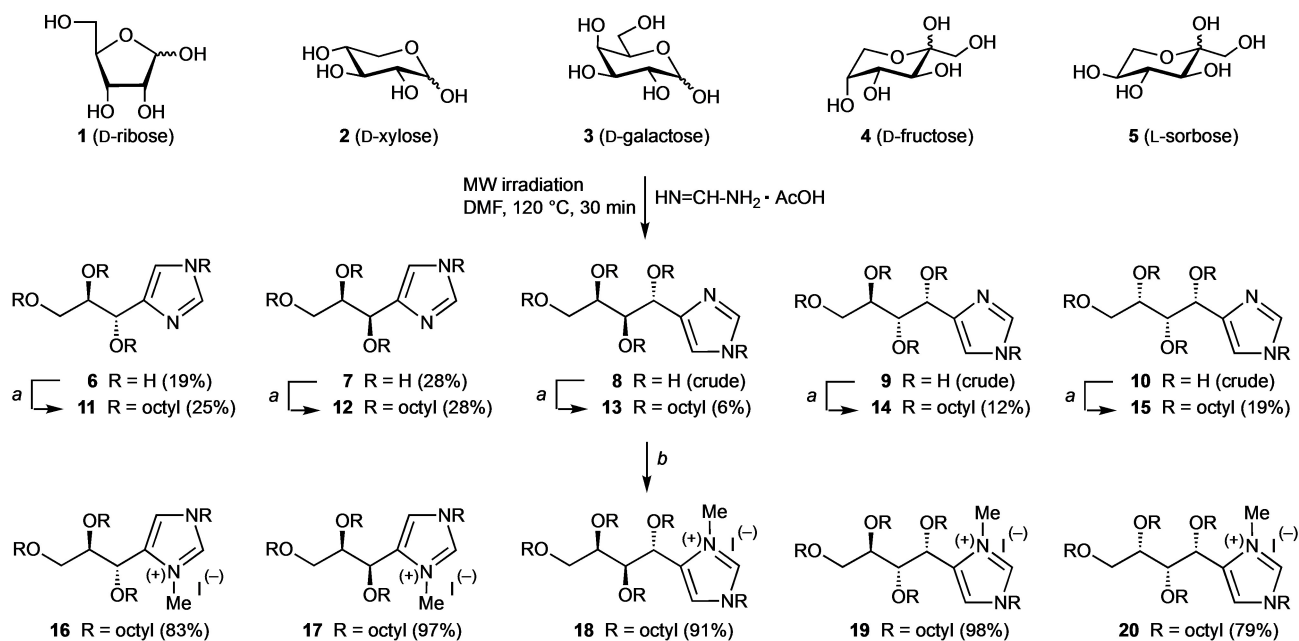
Then, we envisaged to prepare a series of pyrazolium ionic liquids taking advantage of the achiral (**24**) and chiral (**25**) pyrazole derivatives obtained in a multigram scale from D-xylose (**2**) and D-glucose (**21**), respectively, as described[6,7] by Lichtenthaler and co-workers in 1998 (Scheme 2). Upon heating a solution of the monosaccharides **2** and **21** (100 mmol, 15–18 g) in the presence of an excess of phenylhydrazine, the phenylosazones **22** and **23** were isolated in high yield by crystallization. Treatment of the latter with acetic anhydride at reflux afforded the corresponding pyrazole *N*-acetylphenylhydrazone derivatives **24** and **25**, isolated by crystallization.

These compounds were then reacted with formaldehyde to reveal the formyl group which, after saponification, was easily reduced to give the known *N*-phenyl-pyrazole diol **26**[6] and triol **27**,[7] recovered in high yield by column chromatography on silica gel.

Aiming to synthesize new pyrazolium ionic liquids, the diol **26** was *O*-alkylated under standard conditions to afford the dimethyl (**28**) and dioctyl (**29**) ethers that were *N*-alkylated by reaction with methyl triflate to give the achiral ILs **30** and **31**, respectively (Scheme 3). A similar reaction sequence allowed to obtain the methylated and octylated chiral ILs **34** and **35** from the triol **27**. Aiming to prepare more rigid pyrazolium ionic liquids, the latter was converted into the isopropylidene derivative **36** by treatment with 2,2-dimethoxypropane (DMP) and 10-camphorsulfonic acid (CSA). The pyrazole alcohol **36** was directly *N*-methylated to afford the triflate salt **37** or first *O*-alkylated and then *N*-methylated to give the ionic liquids **40** and **41** (Scheme 3).

The third series of sugar-based ionic liquids was prepared from aldaric acids, i.e. dicarboxylic acids obtained by oxidation of both the formyl group and the primary alcohol. The oxidation of D-xylose (**2**) with 70% aqueous nitric acid led to the known[8] xylaric acid (**42**), a *meso* compound, in good yield (Scheme 4). Although the efficient reaction of aldaric acids with 1,2-diaminobenzene leading to bis-benzimidazole derivatives was already described in the literature,[9] we chose to replace the highly toxic *o*-phenylendiamine with the harmless 1,2-diamino-4,5-dimethylbenzene **43**. Thus, a solution of xylaric acid, diamine **43**, and strong acids (HCl and H_3PO_4) in 2-methoxyethanol was refluxed for two hours to afford the bis-benzimidazole **44**. The Williamson methylation of this triol at low temperature afforded the *N,O*-tetramethylated derivative **45** whereas the alkylation at room temperature with 1-bromooctane gave the *N,O*-tetraoctylated derivative **46**. Both ethers were then *N*-methylated with methyl iodide or triflate to give the corresponding *O*-methylated (**47–48**) and *O*-octylated (**49–50**) achiral ionic liquids.

A similar synthetic approach allowed to prepare the enantiopure bis-benzimidazolium ionic liquids **56–61** (Scheme 5). The nitric acid oxidation of D-glucose (**21**) led to D-glucaric acid (**51**) which, upon repeated coevaporation with toluene, afforded the known[10,11] D-glucaro-1,4:6,3-dilactone (**52**). Upon reaction with **43** as described above, the latter was converted into the bis-benzimidazole tetrol **53** that was alkylated to give **54** and **55**. Both compounds were finally treated with three different methylating agents to afford the

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doi.org/10.1002/ejoc.202200100

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Scheme 1. Synthesis of imidazolium ionic liquids from sugars. Reagents and conditions: a) NaH, 1-bromooctane, DMF, r.t., 16 h; b) CH₃I, DMF, 50 °C, 1 h.
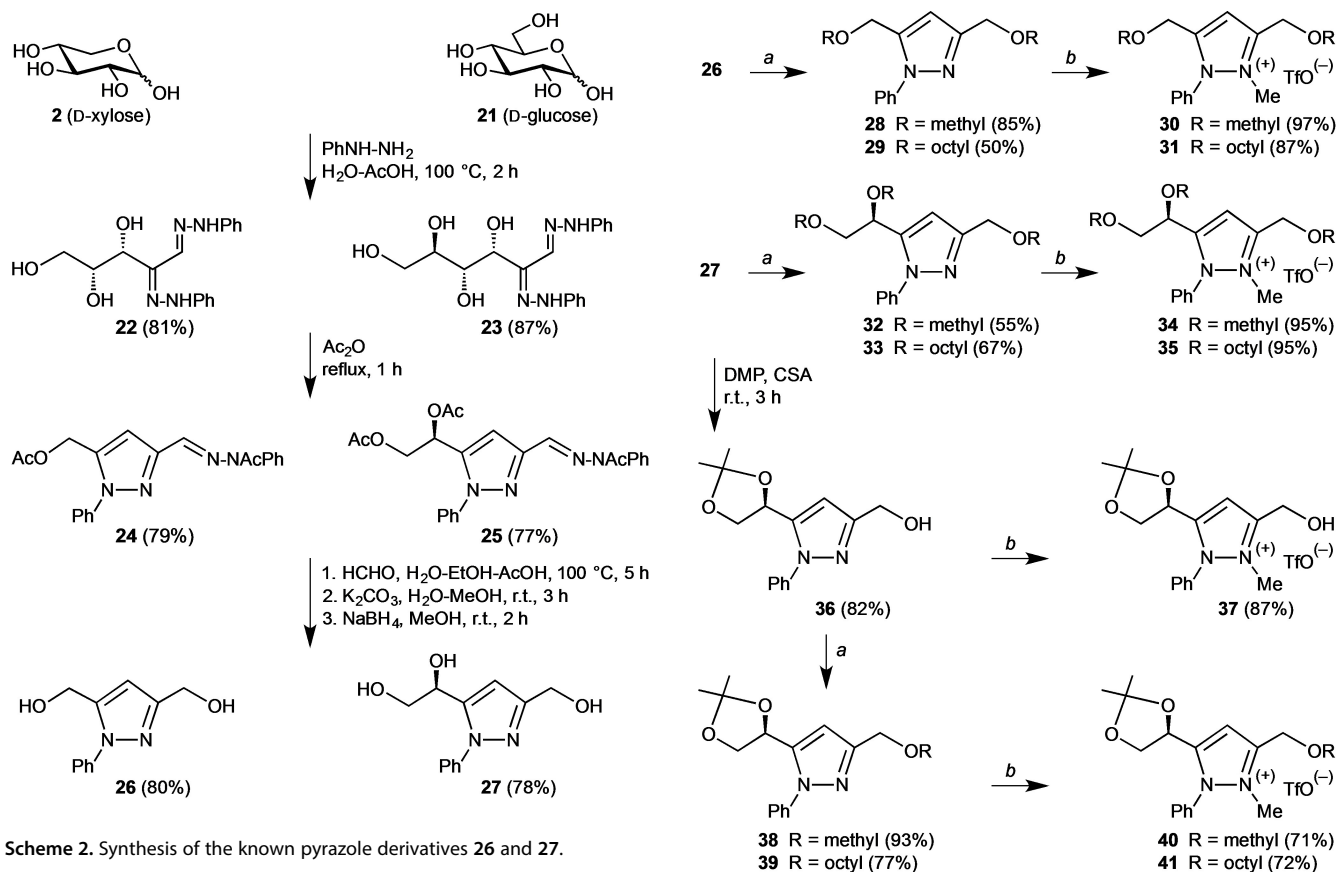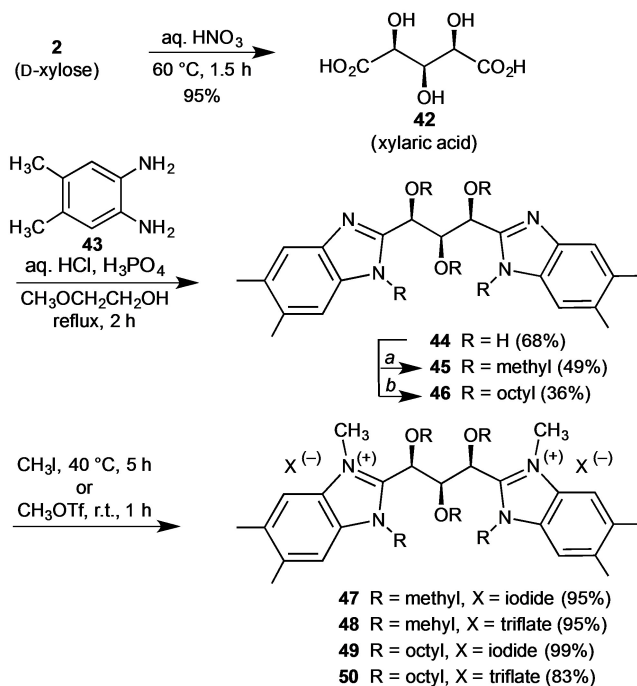

Scheme 2. Synthesis of the known pyrazole derivatives **26** and **27**.

Scheme 3. Synthesis of chiral and achiral pyrazolium ionic liquids from sugars. Reagents and conditions: a) NaH, CH₃I or CH₃(CH₂)₇Br, DMF, r.t., 16 h; b) CH₃OTf, CH₃CN, r.t., 30 min.

corresponding *O*-methylated (**56–58**) and *O*-octylated (**59–61**) ionic liquids bearing iodide, triflate or methylsulfate anion.

A deeper characterization of some representative pyrazolium and bis-benzimidazolium derivatives in view of future

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doi.org/10.1002/ejoc.202200100

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Scheme 4. Synthesis of *meso* bis-benzimidazolium ionic liquids from sugars. Reagents and conditions: a) NaH, CH₃I, DMF, 0 °C, 5 h; b) NaH, CH₃(CH₂)₇Br, DMF, r.t., 16 h.

Scheme 5. Synthesis of chiral bis-benzimidazolium ionic liquids from sugars. Reagents and conditions: a) NaH, CH₃I, DMF, 0 °C, 5 h; b) NaH, CH₃(CH₂)₇Br, DMF, r.t., 16 h.
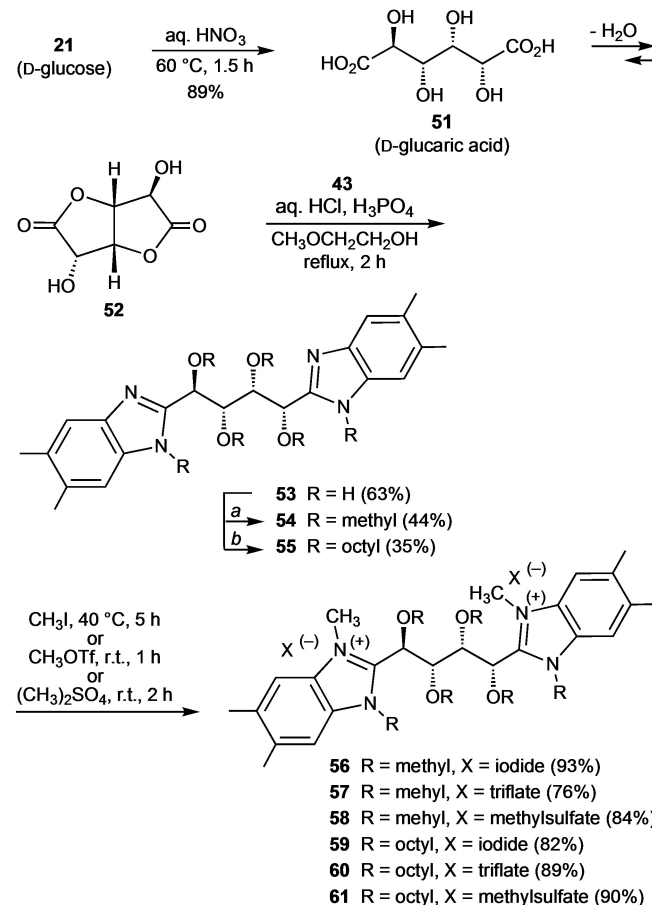
applications as ILs and/or chiral solvents or auxiliaries was performed.

Pyrazolium derivatives

The standard ^{1}H NMR (500 MHz) of **30**, **31**, **34** and **35** are reported in the Supporting Information (Figures S1–S4). The self-diffusion properties and the possible anion-cation aggregations were investigated via pulsed field gradient spin-echo (PFGSE) NMR and NOE correlations spectroscopy. The self-diffusion coefficients D of the pyrazolium ILs **30**, **31**, **34** and **35** are reported in Table 1. The use of ^{1}H and ^{19}F frequency domains in two different arrays of experiments allowed us to measure D(cation) and D(anion), respectively.

The reported values follow the order $D_{30} = D_{34} > D_{31} = D_{35}$ showing a quite predictable ranking on the basis of the molecular weight and hydrodynamic radii. The presence of long alkyl chains on **31** and **35** not only contributes to the molecular weight but also affects the extension of the solvation shell in apolar solvent. Interestingly, the data show D (cation) ≈ D (anion) in all cases, thus providing a first experimental

indication of possible aggregation phenomena. Although this result is referred to the IL dissolved in CDCl₃, the possible formation of ion pairs is a preliminary descriptor useful for the coming up characterization of the pure liquids, especially in terms of polar and apolar domains and their interactions.

Complementary information can be obtained via homo- and heteronuclear NOE correlation spectroscopy, NOESY and HOESY, respectively. The [[1]H-^{1}H] NOESY spectra were recorded with two specific purposes: i) to work out conformational features, if any, and ii) to identify possible intermolecular NOEs, markers of aggregation phenomena. In all cases, the NOESY maps were dominated by intramolecular contact, i.e. dipolar interactions of H nuclei in spatial proximity within the molecular structure of the cations. No evidence of intermolecular NOEs, i.e. interaction related to aggregation phenomena of the cations (e.g. formation of clusters or domains), were detectable. The intramolecular NOESY cross-peaks patterns showed a pattern fully consistent with the expected conformational preferences of the flexible parts of cations **30**, **31**, **34** and **35** on the basis of the known torsional barriers. Thus, no further discussion on [[1]H-^{1}H] NOESY will be reported here. On the other hand, the [[1]H-^{19}F] heteronuclear NOE correlations (HOESY) provided information on the interactions of the cations with the mutual

Table 1. Self-diffusion coefficients D of selected pyrazolium ionic liquids.

IL	D (m²/s) cation	D (m²/s) anion
30	7.5 10⁻¹⁰	7.3 10⁻¹⁰
31	6.1 10⁻¹⁰	6.0 10⁻¹⁰
34	7.4 10⁻¹⁰	7.0 10⁻¹⁰
35	5.8 10⁻¹⁰	5.1 10⁻¹⁰

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anion (triflate). The use of intermolecular NOEs in ionic liquids is currently object of a debate and under rapid development.[12,13] It is sufficient here to remind that the intermolecular contacts detected in ILs systems point to a description of the solvation shell rather than focus on atom-to-atom short contacts. Under this perspective, the HOESY results can be divided into two groups, those obtained from the *O*-methylated ILs **30** and **34**, and those found for the corresponding *O*-octylated derivatives **31** and **35**. The contour maps of the two representative compounds **30** and **35** are reported in the Figure 2 and Figure 3. The ionic liquids **30** and **34** displayed dipolar contact of the CF_3 group of the anion with all hydrogen atoms of the cation, in a totally unselective way (Figure 2). This behavior indicates that anion and cation solvate each other with non-structured solvation shells.

Conversely, the HOESY pattern observed for ILs **31** and **35** was significantly different. In both cases, [^{1}H-^{19}F] HOESY showed cross-peaks connecting the CF_3 group of the anion to the phenyl protons, the pyrazole ring H-4 proton, the octylO-CH_2 groups, and the *N*-CH_3 group of the cation (Figure 3). A good degree of selectivity is observed on the contacts between CF_3 of the anion and the octyl chains of the cation (only one weak cross-peak localized at 1.18 ppm is visible in the contour map). This selective pattern points toward a structured solvation shell, with region of the cation easily accessible to the anion and other parts virtually "forbidden". The different structuration of the solvation shells here mentioned suggests the possibility of
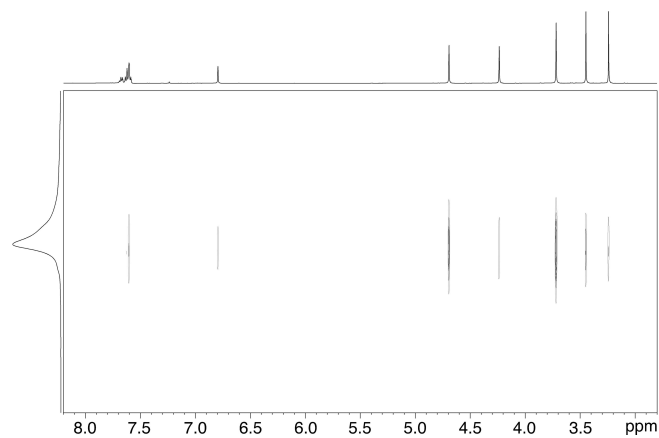
modulating the extension of the polar and apolar domains in the pure liquids, thus giving a structural hint to the rational design of this class of ILs.

Benzimidazolium derivatives

The proton NMR spectra of **56**, **57** and **58** are shown, in a stacked plot representation, in Figure S5. The three compounds share the same cation and differ for the anion. The latter is affecting the magnetic environment of the cation's protons, especially those on the stereogenic carbon atoms. The chemical shift variations as a function of the anion are summarized in Table 2 (see Figure 4 for atom numbering).

One of the two hydrogen atoms (a or a′) of the tetramethoxy-1,4-butandiyl chain linking the two benzimidazolium moieties turned out to be the most sensitive H nucleus to cation – anion interactions, followed by the other hydrogen located at the opposite side (a′ or a). In turn, the perturbation carried out by iodide was larger than those of the structurally similar triflate and methylsulfate, presumably because of the different size and polarizability of the latter two compared to iodide. Overall, the chemical shift variations tend to indicate an interaction cation-anion in apolar solvent even in dilute solution. Further insights came from the determination of the diffusion coefficients via PFGSE NMR. The results are summarized in Table 3. The first three entries refer to the *O*-methylated derivatives **56–58**, while

Figure 2. [^{1}H-^{19}F] HOESY contour map of the ionic liquid **30**.
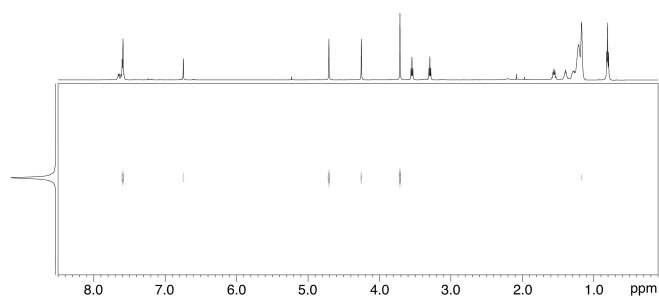
Figure 3. [^{1}H-^{19}F] HOESY contour map of the ionic liquid **35**.

Table 2. Selected chemical shift values of bis-benzimidazolium ILs **56–58**.

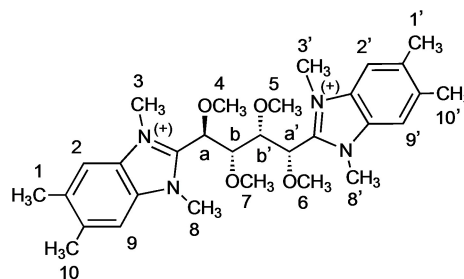| IL	Chemical shifts									
	2,2′	9,9′	a(a′)	a′(a)	3,8	7	5	4	6	1,10
56	7.59	7.48	6.41	5.81	4.31	3.70	3.61	3.37	3.19	2.41
58	7.53	7.47	5.80	5.60	4.22	3.50	3.50	3.31	3.15	2.42
57	7.52	7.46	5.69	5.51	4.21	3.56	3.56	3.30	3.15	2.41

Figure 4. Structure and numbering of the ILs **56–58** cation.

Table 3. Self-diffusion coefficients D of the bis-benzimidazolium ionic liquids.

IL	D (m²/s) cation	D (m²/s) anion
56	1.1×10^{-9}	
58	1.4×10^{-9}	
57	1.1×10^{-9}	1.0×10^{-9}
59	1.1×10^{-9}	
61	1.0×10^{-9}	
60	0.8×10^{-9}	0.9×10^{-9}

the others are referred to the *O*-octylated compounds **59**–**61**. All the measured D are quite similar, thus indicating that the diffusivity is largely dictated by the structure of the cation, with negligible influence of the anion. In the two cases where the D of the anion was obtained, the diffusivity of anion and cation resulted comparable, thus confirming the interaction inferred above from chemical shift data.

Conclusion

Taking advantage of previously described synthetic approaches to sugar-derived aromatic diazaheterocycles, we prepared six achiral ionic liquids and sixteen enantiomerically pure ILs. These compounds featured three different cations (imidazolium, pyrazolium and benzimidazolium ions) and three anions (iodide, triflate and methylsulfate ions), the latter being installed in the ILs simply by using the suitable methylating agent (iodomethane, methyl triflate and dimethyl sulfate) thus avoiding the common, yet sometimes troublesome, anion metathesis.

It is worthy of note that only a very limited number of pyrazolium-based ionic liquids are known, probably because *N*-alkyl-pyrazoles, unlike *N*-alkyl-imidazoles, are quite expensive or not commercially available. Therefore, the seven newly prepared pyrazolium-ILs (see Scheme 3) constitute an interesting extension of this rather neglected class of ionic liquid.

Finally, the chiral and achiral bis-benzimidazolium-ILs synthesized from sugars (see Scheme 4 and Scheme 5) are new members of another small and poorly explored family of solvents when compared to the well-studied bis-imidazolium-ILs. In conclusion, the synthesis on a meaningful scale of the ionic liquids described in the present work should allow to find new properties and applications for these alternative solvents, particularly those containing pyrazolium and bis-benzimidazolium cations. To this aim, studies are underway in our laboratories.

Experimental Section

General procedure for the synthesis of the imidazole derivatives 6–10. A mixture of monosaccharides (10.0 mmol), formamidine acetate (1.25 g, 12.0 mmol) and DMF (3.3 mL) was stirred at 120 °C for 30 min in a single-mode cavity microwave oven (Biotage Initiator) and then concentrated. A solution of the brown residue in water (5 mL) was stirred at room temperature for 1 h with Amberlite IR-120 ion exchange resin (H$^+$ form, 4.5 g, ~20 mmol, activated immediately before the use) and then filtered. The resin was washed with water and the product was desorbed by stirring with a 10% (w/v) solution of ammonia in water at room temperature for 1 h. The resin was removed by filtration, washed with methanol and the solution was concentrated to give the crude imidazole derivatives **6**–**10** as brown syrups.

4-[(1S,2R)-1,2,3-trihydroxy-propyl]-imidazole (6). The reaction of D-ribose (1.500 g) with formamidine acetate gave, after column chromatography on silica gel (1:1 Et$_2$O-MeOH, containing 2% of NH$_3$), **6** as a colorless syrup (300 mg, 19%); $[\alpha]_D = +5.6$ (*c* 1.1, MeOH). ^{1}H NMR (400 MHz, D$_2$O): δ 7.67 (s, 1H, H-2 Im.), 7.00 (s, 1H, H-5 Im.), 4.57 (d, 1H, *J* = 6.5 Hz, H-1), 3.83 (ddd, 1H, *J* = 3.3, 6.5,

7.0 Hz, H-2), 3.61 (dd, 1H, *J* = 3.3, 11.5 Hz, H-3a), 3.44 (dd, 1H, *J* = 7.0, 11.5 Hz, H-3b). ^{13}C NMR (100 MHz, D$_2$O): δ 136.8 (C), 135.8 (CH), 114.9 (CH), 73.6 (CH), 67.4 (CH), 62.4 (CH$_2$). HRMS (ESI) *m/z* calcd for C$_6$H$_{11}$N$_2$O$_3$ (M + H)$^+$ 159.0770, found 159.0772.

1-Octyl-4-[(1S,2R)-1,2,3-trioctanoxy-propyl]-imidazole (11). To a cooled (0 °C), stirred solution of triol **6** (179 mg, 1.13 mmol) in DMF (3 mL) was added NaH (365 mg, 9.1 mmol, of a 60% dispersion in oil) and, after 15 min, 1-bromooctane (1.2 mL, 6.9 mmol). The mixture was stirred at room temperature for 16 h, then diluted with CH$_3$OH (2 mL) and, after 10 min, concentrated. A suspension of the residue in AcOEt (100 mL) was washed with water (2 × 50 mL), dried (Na$_2$SO$_4$) and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 4:1 to 2:1, containing 0.7% of Et$_3$N) to give **11** (169 mg, 25%) as a syrup; $[\alpha]_D = +16.4$ (*c* 1.0, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.40 (s, 1H, H-2 Im.); 6.87 (s, 1H, H-5 Im.); 4.38 (d, 1H, *J* = 5.2 Hz, H-1); 3.86 (t, 2H, *J* = 7.0 Hz, NCH$_2$); 3.80 (ddd, *J* = 3.0, 5.2, 8.5 Hz, 1H, H-2); 3.66–3.34 (m, 8H, 2 H-3, 3 OCH$_2$); 1.80–1.70 (m, 2H, CH$_2$); 1.60–1.40 (m, 6H, 3 CH$_2$); 1.38–1.10 (m, 40H, 20 CH$_2$); 0.92–0.80 (m, 12H, 4 CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 141.0 (C); 136.2 (CH); 117.4 (CH); 81.0 (CH); 76.7 (CH); 71.5 (CH$_2$); 71.2 (CH$_2$); 70.8 (CH$_2$); 69.4 (CH$_2$); 47.0 (CH$_2$); 31.8, 31.7, 31.0, 30.1, 29.8, 29.7, 29.5, 29.3, 29.1, 29.0, 26.5, 26.1, 26.0 and 22.6 (CH$_2$); 14.1 (CH$_3$). HRMS (ESI) *m/z* calcd for C$_{38}$H$_{75}$N$_2$O$_3$ (M + H)$^+$ 607.5778, found 607.5771.

3-Methyl-1-octyl-4-[(1S,2R)-1,2,3-trioctanoxy-propyl]-imidazolium iodide (16). A solution of **11** (111 mg, 0.18 mmol) and iodomethane (57 μL, 0.92 mmol) in DMF (0.5 mL) was stirred at 50 °C for 1 h and then concentrated to give **16** (115 mg, 83%) as a syrup; $[\alpha]_D = +4.6$ (*c* 1.2, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ 10.54 (s, 1H, H-2 Im.); 7.26 (s, 1H, H-5 Im.); 4.52 (d, 1H, *J* = 6.2 Hz, H-1); 4.28 (t, 2H, *J* = 7.0 Hz, NCH$_2$); 4.20 (s, 3H, NCH$_3$); 3.64–3.48 (m, 4H, 2 OCH$_2$); 3.46–3.34 (m, 5H, H-2, 2 H-3, OCH$_2$); 1.98–1.86 (m, 2H, CH$_2$); 1.60–1.40 (m, 6H, 3 CH$_2$); 1.38–1.14 (m, 40H, 20 CH$_2$); 0.92–0.82 (m, 12H, 4 CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 137.3 (CH); 134.0 (C); 119.8 (CH); 79.7 (CH); 72.3 (CH); 71.6 (CH$_2$); 70.9 (CH$_2$); 70.6 (CH$_2$); 68.3 (CH$_2$); 49.8 (CH$_2$); 35.2 (CH$_3$); 31.5, 31.3, 29.8, 29.5, 29.32, 29.28, 29.1, 29.0, 28.7, 28.6, 25.9, 25.8, 25.6 and 22.3 (CH$_2$); 13.8 (CH$_3$). HRMS (ESI) *m/z* calcd for C$_{39}$H$_{77}$N$_2$O$_3$ (M)$^+$ 621.5934, found 621.5937.

3,5-Di(methoxymethyl)-1-phenyl-pyrazole (28). To a cooled (0 °C), stirred solution of diol **26** (500 mg, 2.45 mmol) in DMF (5 mL) was added NaH (390 mg, 9.8 mmol, of a 60% dispersion in oil) and, after 15 min, iodomethane (480 μL, 7.35 mmol). The mixture was stirred at room temperature for 16 h, then diluted with CH$_3$OH (2 mL) and, after 10 min, concentrated. A suspension of the residue in AcOEt (50 mL) was washed with water (2 × 20 mL), dried (Na$_2$SO$_4$) and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 3:1 to 1:1) to give **28** (485 mg, 85%) as a syrup. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.61–7.57 (m, 2H, Ph); 7.49–7.43 (m, 2H, Ph); 7.40–7.35 (m, 1H, Ph); 6.50 (s, 1H, H-4); 4.53 (s, 2H, Pyr-CH$_2$); 4.39 (s, 2H, Pyr-CH$_2$); 3.43 (s, 3H, OCH$_3$); 3.38 (s, 3H, OCH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.8 (C); 139.7 (C); 139.3 (C); 128.9 (CH); 127.6 (CH); 124.3 (CH); 108.1 (CH); 68.1 (CH$_2$); 64.3 (CH$_2$); 58.1 (CH$_3$); 57.6 (CH$_3$). HRMS (ESI) *m/z* calcd for C$_{13}$H$_{17}$N$_2$O$_2$ (M + H)$^+$ 233.1290, found 233.1290.

3,5-Di(octanoxymethyl)-1-phenyl-pyrazole (29). To a cooled (0 °C), stirred solution of diol **26** (0.99 g, 4.85 mmol) in DMF (5 mL) was added NaH (0.78 g, 19.4 mmol, of a 60% dispersion in oil) and, after 15 min, 1-bromooctane (2.52 mL, 14.6 mmol). The mixture was stirred at room temperature for 16 h, then diluted with CH$_3$OH (2 mL) and, after 10 min, concentrated. A suspension of the residue in AcOEt (300 mL) was washed with water (2 × 60 mL), dried (Na$_2$SO$_4$) and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 8:1 to 5:1) to give **29** (1.03 g, 50%) as a syrup. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63–7.58 (m,

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doi.org/10.1002/ejoc.202200100

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2H, Ph); 7.48–7.42 (m, 2H, Ph); 7.39–7.33 (m, 1H, Ph); 6.49 (s, 1H, H-4); 4.56 (s, 2H, Pyr-CH₂); 4.41 (s, 2H, Pyr-CH₂); 4.52 (t, 2H, $J = 6.8$ Hz, OCH₂); 3.46 (t, 2H, $J = 6.5$ Hz, OCH₂); 1.66–1.54 (m, 4H, 2 CH₂); 1.40–1.20 (m, 20H, 10 CH₂); 0.91–0.84 (m, 6H, 2 CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 150.4 (C); 140.2 (C); 139.6 (C); 129.0 (CH); 127.6 (CH); 124.4 (CH); 108.2 (CH); 70.7, 66.6, 62.9, 31.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.3, 26.2, 22.6 (CH₂); 14.1 (CH₃). HRMS (ESI) *m/z* calcd for C₂₇H₄₅N₂O₂ (M + H)⁺ 429.3481, found 429.3472.

3,5-Di(methoxymethyl)-1-methyl-2-phenyl-pyrazolium triflate (30). A mixture of **28** (444 mg, 1.91 mmol), activated 4 Å powdered molecular sieve (0.20 g), and anhydrous CH₃CN (2.5 mL) was stirred for 10 min at room temperature, then methyl triflate (325 µL, 2.87 mmol) was added. The mixture was stirred for 30 min, filtered through a pad of Celite, and concentrated. A solution of the residue in CHCl₃ (100 mL) was washed with water (20 mL) and concentrated to give **30** (734 mg, 97%) as a syrup. ¹H NMR (400 MHz, CDCl₃): δ 7.80–7.60 (m, 5H, Ph); 6.81 (s, 1H, H-4); 4.67 (s, 2H, Pyr-CH₂); 4.25 (s, 2H, Pyr-CH₂); 3.79 (s, 3H, NCH₃); 3.48 (s, 3H, CH₃); 3.28 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 148.0 (C); 147.2 (C); 133.1 (CH); 130.8 (CH); 130.3 (C); 128.7 (CH); 107.8 (CH); 64.9 (CH₂); 64.5 (CH₂); 59.4 (CH₃); 59.0 (CH₃); 35.4 (CH₃). HRMS (ESI) *m/z* calcd for C₁₄H₁₉N₂O₂ (M)⁺ 247.1446, found 247.1453.

3-Hydroxymethyl-5-[(1′S)-1′,2′-isopropylidenoxy-ethyl]-1-phenyl-pyrazole (36). A solution of **27** (1.22 g, 5.21 mmol) and camphorsulfonic acid (130 mg) in 2,2-dimethoxypropane (26 mL) was kept at room temperature for 3 h, then diluted with Et₃N (0.5 mL) and concentrated. To a solution of the residue in CH₃OH (30 mL) was added enough camphorsulfonic acid to reach pH 2 and the solution was kept at room temperature for ca. 10 min in order to cleave the mixed ketal formed at the primary position without removing the isopropylidene group (tlc analysis), then diluted with an excess of Et₃N and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 1:1 to 1:2, containing 2% of Et₃N) to give **36** (1.17 g, 82%) as a syrup; $[\alpha]_D = -15.0$ (*c* 0.3, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ 7.60–7.40 (m, 5H, Ph); 6.55 (s, 1H, H-4); 5.03 (dd, 1H, $J = 6.5, 6.5$ Hz, H-1′); 4.77 (s, 2H, Pyr-CH₂); 4.20 (dd, 1H, $J = 6.5, 8.5$ Hz, H-2′a); 4.03 (dd, 1H, $J = 6.5, 8.5$ Hz, H-2′b); 2.00 (s, 1H, OH); 1.52 (s, 3H, CH₃); 1.43 (s, 3H, CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 152.9 (C); 142.1 (C); 139.0 (C); 129.2 (CH); 128.3 (CH); 125.2 (CH); 110.3 (C); 104.2 (CH); 69.4 (CH₂); 69.4 (CH); 58.9 (CH₂); 26.7 (CH₃); 25.8 (CH₃). HRMS (ESI) *m/z* calcd for C₁₅H₁₉N₂O₃ (M + H)⁺ 275.1396, found 275.1393.

(1R,2r,3S)-1,3-Bis(5,6-dimethylbenzimidazol-2-yl)-1,2,3-propan-triol (44). A mixture of xylaric acid **42** (2.50 g, 13.88 mmol), diamine **43** (4.91 g, 36.08 mmol), HCl (3.0 mL, 36.5 mmol, of a 37% solution in H₂O), H₃PO₄ (2.5 mL, 36.5 mmol, of an 85% solution in H₂O), and 2-methoxyethanol (6 mL) was stirred at 140°C for 2 h, then cooled to room temperature. The solution was diluted with water (20 mL) and 1 M aqueous HCl (2.5 mL), stirred at 120°C for 1 h in the presence of activated vegetal charcoal (ca. 1.0 g), cooled to room temperature, and filtered through Celite. The pale-yellow solution was cooled to 0°C and basified with a 30% solution of ammonia in H₂O to precipitate a solid that was filtered off, washed with cold water, and dried under vacuum to give crude **44**. Trituration of the yellow solid with acetone afforded pure **44** (3.59 g, 68%) as a white solid; m.p. 212–216°C (decomp.). ¹H NMR (200 MHz, DMSO-d_6 + D₂O, 120°C): δ 7.29 (s, 4H, Ar); 5.00 (d, 2H, $J = 4.6$ Hz, H-1, H-3); 4.26 (t, 1H, $J = 4.3$ Hz, H-2); 2.30 (s, 12H, 4 CH₃). ¹³C NMR (100 MHz, DMSO-d_6): δ 155.1 (C); 130.1 (C); 115.1 (CH); 75.6 (CH); 68.3 (CH); 20.2 (CH₃). HRMS (ESI) *m/z* calcd for C₂₁H₂₅N₄O₃ (M + H)⁺ 381.1927, found 381.1919.

(1R,2r,3S)-1,3-Bis(1,5,6-trimethylbenzimidazol-2-yl)-1,2,3-trimeth-oxy-propane (45). To a cooled (0°C), stirred solution of triol **44** (519 mg, 1.37 mmol) in DMF (5 mL) was added NaH (546 mg, 13.7 mmol, of a 60% dispersion in oil) and, after 15 min, iodo-methane (510 µL, 8.19 mmol). The mixture was stirred at 0°C for 5 h, then diluted with CH₃OH (1 mL) and, after 10 min, concentrated. A suspension of the residue in AcOEt (60 mL) was washed with 1 M phosphate buffer at pH 7 (2 × 10 mL), dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with AcOEt-acetone (from 8:1 to 3:1) to give **45** (300 mg, 49%) as a syrup. ¹H NMR (400 MHz, CDCl₃): δ 7.41 (s, 2H, Ar); 6.90 (s, 2H, Ar); 4.65 (d, 2H, $J = 6.5$ Hz, H-1, H-3); 4.24 (t, 1H, $J = 6.5$ Hz; H-2); 3.85 (s, 6H, 2 CH₃); 3.42 (s, 3H, CH₃); 3.24 (s, 6H, 2 CH₃); 2.34 (s, 6H, 2 Ar-CH₃); 2.33 (s, 6H, 2 Ar-CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 149.7 (C); 140.5 (C); 134.8 (C); 131.9 (C); 130.8 (C); 119.4 (CH); 109.5 (CH); 85.4 (CH); 79.4 (CH); 61.5 (CH₃); 57.5 (CH₃); 30.3 (CH₃); 20.5 (CH₃); 20.2 (CH₃). HRMS (ESI) *m/z* calcd for C₂₆H₃₅N₄O₃ (M + H)⁺ 451.2709, found 451.2700.

(1R,2r,3S)-1,3-Bis(5,6-dimethyl-1-octyl-benzimidazol-2-yl)-1,2,3-tri-octanoxy-propane (46). To a cooled (0°C), stirred solution of triol **44** (527 mg, 1.39 mmol) in DMF (5 mL) was added NaH (555 mg, 13.9 mmol, of a 60% dispersion in oil) and, after 15 min, 1-bromooctane (1.81 mL, 10.4 mmol). The mixture was stirred at room temperature for 16 h, then diluted with CH₃OH (1 mL) and, after 10 min, concentrated. A suspension of the residue in AcOEt (60 mL) was washed with 1 M phosphate buffer at pH 7 (2 × 10 mL), dried (Na₂SO₄) and concentrated. The residue was eluted from a column of silica gel with cyclohexane-AcOEt (from 10:1 to 3:1) to give **46** (470 mg, 36%) as a syrup. ¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 2H, Ar); 6.77 (s, 2H, Ar); 4.73 (d, 2H, $J = 6.8$ Hz, H-1, H-3); 4.40 (t, 1H, $J = 6.8$ Hz, H-2); 4.35–4.20 (m, 2H, OCH₂); 4.10–4.00 (m, 2H, OCH₂); 3.57 (t, 2H, $J = 7.0$ Hz, OCH₂); 3.35–3.20 (m, 4H, 2 NCH₂); 2.33 (s, 6H, 2 Ar-CH₃); 2.30 (s, 6H, 2 Ar-CH₃); 1.85–1.10 (m, 60H, 30 CH₂); 0.90–0.80 (m, 15H, 5 CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 150.0 (C); 140.8 (C); 133.9 (C); 131.3 (C); 130.2 (C); 119.4 (CH); 109.8 (CH); 83.2 (CH); 77.4 (CH); 74.3 (CH₂); 70.6 (CH₂); 44.5 (CH₂); 31.8, 31.8, 30.2, 29.8, 29.7, 29.5, 29.4, 29.3, 29.2, 27.1, 26.0, 22.3 (CH₂); 20.5 (CH₃); 20.2 (CH₃); 14.0 (CH₃). HRMS (ESI) *m/z* calcd for C₆₁H₁₀₅N₄O₃ (M + H)⁺ 941.8187, found 941.8176.

(1R,2r,3S)-1,3-Bis(1,3,5,6-tetramethylbenzimidazolium-2-yl)-1,2,3-trimethoxy-propane diiodide (47). A solution of **45** (70 mg, 0.16 mmol) and iodomethane (190 µL, 3.12 mmol) in acetonitrile (1 mL) was stirred at 40°C for 5 h and then concentrated to give **47** (108 mg, 95%) as a syrup. ¹H NMR (400 MHz, CDCl₃): δ 7.47 (s, 4H, Ar); 6.52 (d, 2H, $J = 2.9$ Hz, H-1, H-3); 5.08 (t, 1H, $J = 2.9$ Hz, H-2); 4.39 (s, 12H, 4 NCH₃); 3.68 (s, 6H, 2 OCH₃); 3.39 (s, 3H, OCH₃); 2.41 (s, 12H, 4 Ar-CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 146.2 (C); 137.8 (C); 130.6 (C); 112.5 (CH); 81.2 (CH); 75.3 (CH); 61.7 (CH₃); 59.5 (CH₃); 34.6 (CH₃); 20.6 (CH₃). HRMS (ESI) *m/z* calcd for C₂₈H₄₀N₄O₃/2 (M)²⁺ 240.1550, found 240.1567.

(1R,2r,3S)-1,3-Bis(1,3,5,6-tetramethylbenzimidazolium-2-yl)-1,2,3-trimethoxy-propane ditriflate (48). A mixture of **45** (82 mg, 0.18 mmol), activated 4 Å powdered molecular sieve (0.10 g), and anhydrous CH₃CN (2.5 mL) was stirred for 10 min at room temperature, then methyl triflate (62 µL, 0.54 mmol) was added. The mixture was stirred at room temperature for 1 h, filtered through a pad of Celite, and concentrated. A solution of the residue in CHCl₃ (50 mL) was washed with water (10 mL) and concentrated to give **48** (134 mg, 95%) as a syrup. ¹H NMR (400 MHz, CDCl₃): δ 7.47 (s, 4H, Ar); 5.70 (d, 2H, $J = 3.8$ Hz; H-1, H-3); 4.59 (t, 1H, $J = 3.8$ Hz, H-2); 4.20 (s, 12H, 4 NCH₃); 3.48 (s, 6H, 2 OCH₃); 3.32 (s, 3H, OCH₃); 2.44 (s, 12H, 4 Ar-CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 145.6 (C); 138.0 (C); 130.7 (C); 112.5 (CH); 82.0 (CH); 74.9 (CH); 60.9 (CH₃); 59.1 (CH₃); 33.0 (CH₃); 20.5 (CH₃). HRMS (ESI) *m/z* calcd for C₂₈H₄₀N₄O₃/2 (M)²⁺ 240.1550, found 240.1546.

(1R,2R,3R,4S)-1,4-Bis(5,6-dimethylbenzimidazol-2-yl)-1,2,3,4-bu-tantetrol (53). A mixture of dilactone **52** (2.00 g, 11.49 mmol),

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doi.org/10.1002/ejoc.202200100

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diamine **43** (4.07 g, 29.87 mmol), HCl (2.5 mL, 29.5 mmol, of a 37% solution in H_2O), H_3PO_4 (2.5 mL, 29.5 mmol, of an 85% solution in H_2O), and 2-methoxyethanol (5 mL) was stirred at 140 °C for 2 h, then cooled to room temperature. The solution was diluted with water (20 mL) and 1 M aqueous HCl (2.5 mL), stirred at 120 °C for 1 h in the presence of activated vegetal charcoal (ca. 1.2 g), cooled to room temperature, and filtered through Celite. The pale-yellow solution was cooled to 0 °C and basified with a 30% solution of ammonia in H_2O to precipitate a solid that was filtered off, washed with cold water, and dried under vacuum to give crude **52**. Trituration of the yellow solid with acetone afforded pure **53** (2.90 g, 63%) as an amorphous white solid; $[\alpha]_D = -25.0$ (*c* 0.6, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD): δ 7.30 (s, 2H, Ar); 7.28 (s, 2H, Ar); 5.06 (d, 1H, *J* = 6.2 Hz, H-1 or H-4); 4.96 (d, 1H, *J* = 7.5 Hz, H-1 or H-4); 4.24 (dd, 1H, *J* = 1.9, 6.2 Hz, H-2 or H-3); 3.87 (dd, 1H, *J* = 1.9, 7.5 Hz, H-2 or H-3); 2.35 (s, 6H, 2 Ar-CH₃); 2.34 (s, 6H, 2 Ar-CH₃). ^{13}C NMR (75 MHz, CD_3OD): δ 156.1 (C); 155.3 (C); 136.8 (C); 133.0 (C); 132.8 (C); 115.7 (CH); 115.6 (CH); 74.1 (CH); 73.7 (CH); 71.3 (CH); 69.8 (CH); 20.4 (CH₃). HRMS (ESI) *m/z* calcd for $C_{22}H_{27}N_4O_4$ $(M+H)^+$ 411.2032, found 411.2032.

(1R,2R,3R,4S)-1,4-Bis(1,3,5,6-tetramethylbenzimidazolium-2-yl)-1,2,3,4-tetramethoxy-butane di(methylsulfate) (58). A mixture of **54** (208 mg, 0.42 mmol), activated 4 Å powdered molecular sieve (0.20 g), and anhydrous CH_3CN (2 mL) was stirred for 10 min at room temperature, then dimethyl sulfate (120 μL, 1.26 mmol) was added. The mixture was stirred at room temperature for 2 h, filtered through a pad of Celite, and concentrated to give **58** (265 mg, 84%) as a syrup; $[\alpha]_D = +27.6$ (*c* 0.8, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD): δ 7.79 (s, 2H, Ar); 7.77 (s, 2H, Ar); 5.54 (d, 1H, *J* = 9.0 Hz, H-1 or H-4); 5.48 (d, 1H, *J* = 2.7 Hz, H-1 or H-4); 4.26 (dd, 1 h, *J* = 6.8, 9.0 Hz, H-2 or H-3); 4.24 (s, 12H, 4 CH₃); 4.16 (dd, 1H, *J* = 2.7, 6.8 Hz, H-2 or H-3); 3.57, 3.46, 3.35, 3.17 (4 s, 12H, 4 Ar-CH₃); 3.53 (s, 6H, 2 CH₃); 3.52 (s, 6H, 2 CH₃). ^{13}C NMR (100 MHz, CD_3OD): δ 148.8, 148.3, 139.0, 138.7, 132.2, 132.1 (C); 113.7 (CH); 83.9, 81.4, 77.6, 76.8 (CH); 61.5, 61.4, 59.6, 59.4 (CH₃); 33.3 (CH₃); 20.6 (CH₃). HRMS (ESI) *m/z* calcd for $C_{30}H_{44}N_4O_4/2$ $(M)^{2+}$ 262.1681, found 262.1676.

The experimental procedures and physical data for the other new compounds as well as the copies of ^{1}H-, ^{13}C- and ^{19}F-NMR spectra for all new products can be found in the Supporting Information.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

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