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Novel carbohydrate-based chiral ammonium ionic liquids derived from isomannide

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Abstract—This report describes the synthesis and characterization of novel carbohydrate-based chiral ammonium ionic liquids using isomannide as a biorenewable substrate. The diastereomeric interactions of these chiral ammonium ionic liquids with racemic Mosher's acid salt have been studied using NMR, which indicates their participation in chiral discrimination and shows their potential applications in chiral resolution.

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1. Introduction

Over the past decade, ionic liquids (ILs) have attracted considerable attention as promising materials for a variety of applications.[1] Ionic liquids (salts having a melting point below 100 °C) possess the advantages such as negligible vapor pressure, high thermal stability, and recyclability, which makes them the prominent candidate to replace conventional volatile organic solvents (VOC's). The possibilities of structural variation offer a flexibility to design the most idealized solvent suitable for the needs of any particular process. Apart from tunable physical and chemical properties of ionic liquids, their immiscibility with various organic solvents enables the biphasic separation of the desired products and recycling of expensive catalysts.[1] Furthermore, their ability to dissolve complex molecules such as nucleosides and amino acids allows the chemists to perform chemo- and enantioselective reactions on these compounds under milder conditions.[2] In addition to their utility in organic synthesis, ILs have been studied in bioprocessing operations,[3] as electrolytes in electrochemistry,[4] in gas separations,[5] in liquid–liquid extractions,[6] and as heat-transfer fluids.[7]

Important progress over the past few years with the development of chiral ionic liquids (CILs) has given a new dimension to ionic liquid-based research.[8] Though the CILs are at an early stage of development, they have shown promising results in asymmetric synthesis,[9] stereoselective polymerization,[10] chiral chromatography,[11] liquid crystals,[12] chiral resolution, and as NMR shift reagents.[13] One of the efficient and convenient method to synthesize CILs uses substrates derived from a chiral pool, especially from biorenewable sources. Chiral precursors viz. (−)-ephedrine,[13a,14] (*S*)-nicotine,[15] (−)-menthol,[9b,10c,16] (+)-pinocarvone,[17] and amino acids[13b,18] have been used for the synthesis of CILs. Previously we reported the first synthesis of CILs based on α-pinene and their applications as co-solvents for the enantioselective addition of diethylzinc to enones.[9f] Carbohydrate-based ligands have played a significant role in enantioselective organic transformations.[19] However, the synthesis of CILs from carbohydrate-based substrates is yet to be explored.

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Isomannide **1** and isosorbide **2** are commercially available chiral dianhydrohexitols (Fig. 1). They can be easily prepared in enantiomerically pure form by double dehydration of sorbitol and mannitol, which are major byproducts of the starch industry: Both are obtained in large amounts as waste during the processing of corn oil. These compounds have been used as starting materials for the synthesis of biodegradable and high T_g polymers,[20] pharmaceutically important compounds including vasodilators and Xa-inhibitors,[21] and as chiral ligands or as phase-transfer catalysts in asymmetric synthesis.[22] Surprisingly however, despite their easy availability from a renewable and inexpensive source, there are very few examples of their application as chiral auxillaries[23] and in the synthesis of CILs.[24] We have recently completed the synthesis of bis(ammonium) CILs derived from isomannide (Fig. 2) and demonstrated their application as chiral shift reagents.[25] Herein, we report our extended studies on the synthesis of a new series of mono-ammonium CILs derived from isomannide and their application for chiral recognition.

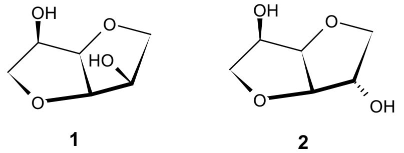
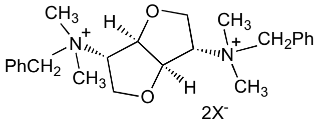


Figure 1. Isomannide **1** amd isosorbide **2**.

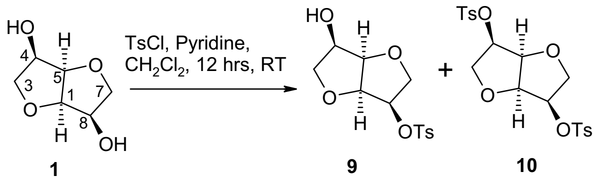


3: X = I
4: X = Tf$_2$N
5: X = PF$_6$
6: X = CF$_3$COO
7: X = BF$_4$
8: X = CF$_3$SO$_3$

Figure 2. Bis-ammonium CILs derived from isomannide.

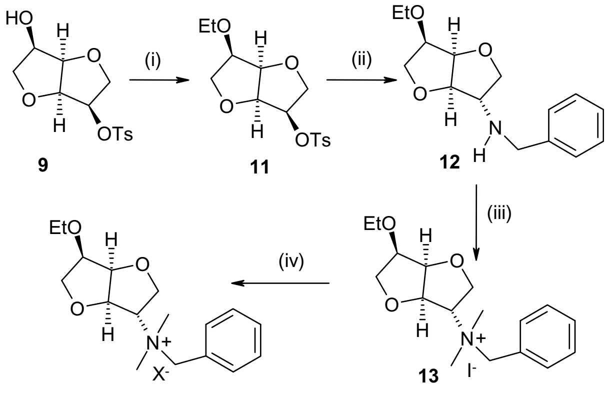
2. Results and discussion

The substitution reaction of isosorbide gives three products (two monosubstituted and one disubstituted) due to its unsymmetrical stereochemistry, which makes the purification and isolation of the products more tedious. Thus, for our current study, we chose isomannide as the starting material due to its preferential stereochemistry. Isomannide is a symmetrical molecule with C_2-axial symmetry comprising of two *cis*-fused furan rings and two *cis*-oriented hydroxyl groups with both the heterocyclic rings and two hydroxyl groups in same plane. Substitution of isomannide gives only two products, i.e., monosubstituted major product and the sterically unfavorable disubstituted as a minor product (Scheme 1).



Scheme 1. Tosylation of isomannide.

Our primary objective was to convert one of the hydroxyl groups of isomannide to a quaternary ammonium salt, which could be further subjected to anion exchange reactions to make a series of chiral ionic liquids. D-Isomannide, also known as (1*R*,4*R*,5*R*,8*R*)-2,6-dioxabicyclo [3.3.0] octan-4,8-diol **1** was first reacted with *p*-toulenesulfonyl chloride under basic medium using pyridine/CH_2Cl_2 (~1:3) as a solvent to give monotosyl derivative **9** as the major product and ditosyl derivative **10** as the minor product. The ditosyl isomannide was utilized for the synthesis of bis(ammonium) CILs (Fig. 2).[25] The free hydroxyl group of monotosyl isomannide **9** was converted to its ethyl ether derivative **11** by reaction with ethyl bromide under basic conditions using tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst (Scheme 2). Subsequently, **11** was converted to amino ether **12** by heating with benzylamine (in excess) at 180 °C.[22a,26] As a result, the tosyloxy group was removed as a salt of benzylamine. This is an exclusive S_N2 substitution causing complete inversion, which was confirmed by comparing the coupling constant between C-1H and C-8H of compounds **11** [$J(H_1, H_8)_{cis} = 4.5$ Hz] and **12** [$J(H_1,H_8)_{trans} = 0$ Hz] from their ^{1}H NMR spectrum. Due to this inversion of configuration, the isomannide nucleus was converted to isosorbide. The *sec*-amine **12** was then directly quaternized to its ammonium iodide salt **13** by treatment with methyl iodide using potassium carbonate as the base. The structure and stereochemistry of **13** was established by ^{1}H, ^{13}C NMR spectroscopy and further confirmed by anomalous dispersion (Fig. 3). The chiral ammonium iodide salt **13**



14; X = (CF$_3$SO$_2$)$_2$N
15; X = PF$_6$
16; X = CF$_3$COO
17; X = BF$_4$
18; X = CF$_3$SO$_3$

Scheme 2. Synthesis of mono-ammonium CILs. Reagents and conditions: (i) EtBr, TBAB, 50% KOH, CH_2Cl_2, rt; (ii) Benzylamine, 180 °C, 12 h; (iii) MeI, K_2CO_3, CH_3CN, rt; (iv) anion metathesis: AgX, H_2O, 50 °C.

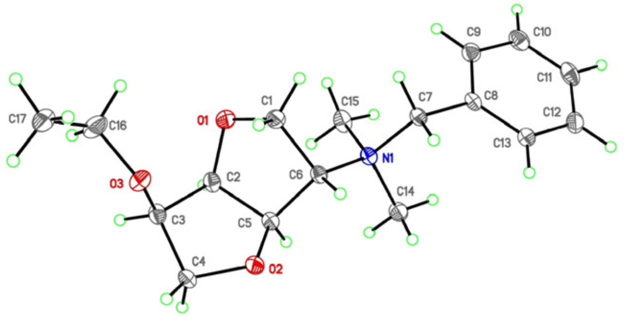


Figure 3. X-ray crystal structure of the cationic part of CIL **13**.[‡]

Table 1. Melting point comparison of mono- and bis-ammonium CILs

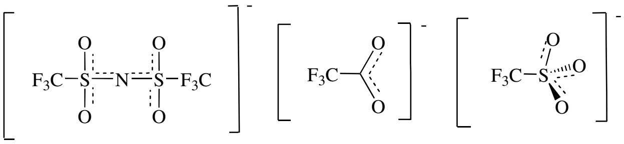
Entry	Anion	Mono-ammonium		Bis-ammonium[25]	
		CILs	Mp (°C)	CILs	Mp (°C)
1	[I]	**13**	170	**3**	190
2	[Tf_2N]	**14**	Oil	**4**	60
3	[PF_6]	**15**	95	**5**	251
4	[TFA]	**16**	Oil	**6**	65
5	[BF_4]	**17**	150	**7**	240
6	[TfO]	**18**	80	**8**	75

was used for anion exchange reactions to obtain other chiral salts with different anions. The anion exchange reactions were carried out in an aqueous medium.

The solubility of iodide salt **13** is low in water at room temperature, therefore, reactions were carried out at 50–60 °C; the iodide salt **13** was completely soluble at this temperature. Thus, the desired mono-ammonium CILs **13**–**18** were synthesized following a simple and convenient methodology involving simple functional group interconversions followed by anion exchange (Scheme 2).

The melting point comparison of all the mono-ammonium CILs and bis-ammonium CILs is given in Table 1. It has been well reported in the literature that the ionic liquids with unsymmetrical cations or anions have low melting points in comparison to the ILs that have symmetrical cations or anions.[27] Increasing symmetry of ions allows more efficient packing in the crystal cells and provides high lattice energy, resulting in an increase in the melting point. Conversely, the loss of symmetry causes crystallographic disorder and reduces the lattice energy, which results in low melting points of ionic liquids with unsymmetrical cations. The bis-ammonium salts **3**–**8** consist of a highly symmetrical cation with C_2-axial symmetry and identical substituents. On the other hand, mono-ammonium salts **13**–**18** are completely unsymmetrical with a nucleus having two different groups attached at the two ends of the molecule. This could be one of the reasons that bis-ammonium salts have high melting points when compared to those of the mono-ammonium salts (Table 1). Generally, the ionic liquids with a high molecular weight have a greater number of intermolecular contacts, which can raise their melting points and viscosity. The high molecular weight of the cation of bis-ammonium salts in comparison with the cation of the mono-ammonium salts could also contribute to high melting points of bis-ammonium salts[27] (except in the case of [TfO] as an anion).

The anion also has a major effect on the physical properties of ionic liquids including the melting point.[27] There is a very complex and poorly understood relationship between the anion and cation size, degree of interaction (both ionic and hydrogen bonding), packing, etc. that relates the physical properties of ionic liquids to their chemical structure.[26] Ionic liquids with bulky and weakly coordinating anions are known to have lower melting points. The Coulombic interactions between cation and anion are also important. In general, the lower the interaction between cation and anion, the lower the melting point. These Coulombic interactions can be minimized by diffusing the charge over several atoms in a molecule.[27,28] The [Tf_2N] anion combines a number of structural features to give the resultant salts low melting points. This could be the reason that most of the ionic liquids with a [Tf_2N] anion are liquid at room temperature. The charge on the [Tf_2N] anion is particularly diffused and spread through the S–N–S core and partially to the trifluoromethane groups as well. Similar charge diffusion is also present in [TFA] and [TfO] anions where the negative charge is spread over O–C–O, and O–SO_2 moieties, respectively (Fig. 4). This diffusivity results in a decreased interaction between the cation and the anion. Thus, in the case of both the mono-ammonium and bis-ammonium ionic liquids, the salts with weakly coordinating anions, viz. [Tf_2N], [TFA], and [TfO], which can delocalize the charge through induction to highly electronegative fluorine atoms or by resonance, have lower melting points when compared to those having [I], [PF_6], and [BF_4] as counter ions (Table 1).



$(CF_3SO_2)_2N^-$
[Tf_2N]

CF_3COO^-
[TFA]

$CF_3SO_3^-$
[TfO]

Figure 4. Delocalization of negative charge on [Tf_2N], [TFA], and [TfO] anions.

Having synthesized these chiral ionic liquids, we were interested in their utility for chiral induction. The enantiomeric recognition ability of any chiral catalyst/promoter/solvent is the most important property for their application in asymmetric induction. We studied the chiral recognition ability of these novel mono-ammonium CILs by investigating the diastereomeric interaction between the CILs and racemic Mosher's acid silver salt. Iodide salt **13** was dissolved in deuterated acetonitrile and stirred with racemic Mosher's acid silver salt. The AgI precipitate was filtered off and the resulting solution containing Mosher's acid

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[‡] The CIF files of X-ray data can be accessed through http://www.ccdc.cam.ac.uk (deposition number CCDC 652067).

chiral ammonium salt **A** was probed by ^{19}F NMR spectroscopy. The diastereomeric interactions between the chiral ammonium cation and Mosher's carboxylate resulted in splitting of the CF_3 signal (Fig. 5, spectrum (a)). When the same NMR solution was mixed with 3.5 equiv of CIL **14**, a remarkable increase in chemical shift value ($\Delta\delta$) of CF_3 signal was observed (Fig. 5, spectrum (b)).

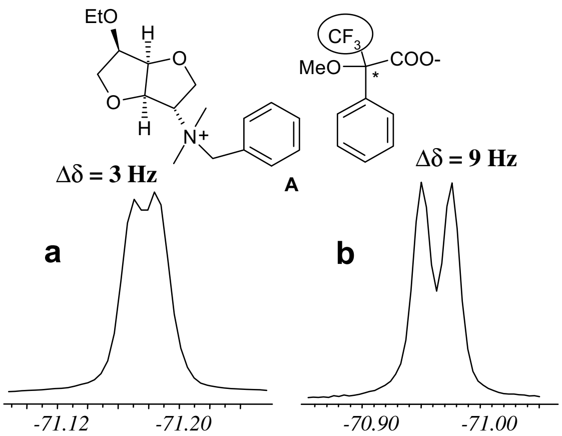

Figure 5. ^{19}F NMR signal of $-CF_3$ of salt **A** (a) and salt **A** in the presence of 3.5 equiv of CIL **14**.

Our previous work[9f] and another report[9e] suggest that the achiral anion may have some effect on the chiral discrimination induced by the CILs. This prompted us to investigate the effect of anions on the diastereomeric interactions between CILs and Mosher's carboxylate. We carried out similar ^{19}F NMR experiments in the presence of all other CILs (as done with $[Tf_2N]$). The results are compared with those of bis-ammonium CILs and summarized in Table 2. These results prove the effect of the cation and anion on the chiral discrimination ability of these CILs, which is indicated by the enhancement in the magnitude of $\Delta\delta$ values (Table 2).

Table 2. Enhanced $\Delta\delta$ values of $-CF_3$ signals of rac-Mosher's carboxylate in the presence of mono- (3.5 equiv) and bis-ammonium (4.0 equiv) CILs

Entry	Anion	Mono-ammonium		Bis-ammonium[25]	
		CILs	$\Delta\delta$ (Hz)	CILs	$\Delta\delta$ (Hz)
1	[I]	**13**	7	**3**	9
2	$[Tf_2N]$	**14**	9	**4**	23
3	$[PF_6]$	**15**	8	**5**	21
4	[TFA]	**16**	5	**6**	8
5	$[BF_4]$	**17**	5	**7**	17
6	[TfO]	**18**	9	**8**	15

The chemical shift induced by the CILs is highly dependent on the concentration of chiral IL present in the NMR solution.[13a] We studied the concentration effect of CIL **14** on the chemical shift difference (indicated by the $\Delta\delta$ values) of two diastereomeric $-CF_3$ groups as described in Figure 6. The results show that as the concentration of chiral IL increased, the chemical shift differences ($\Delta\delta$ values) also increase. A significant increment of 6.1 Hz in the $\Delta\delta$ value of $-CF_3$ signals of racemic Mosher's carboxylate was observed when increasing the concentration of Chiral IL **14** from 0 to 0.81 mol/L.

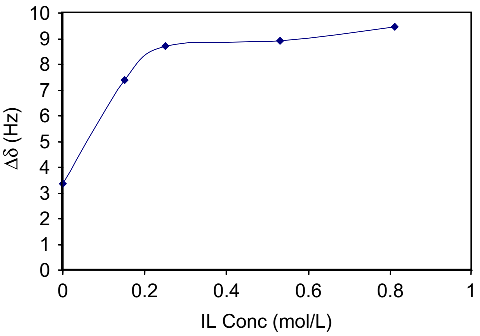

Figure 6. Concn effect of CIL **14** on the $\Delta\delta$ values of $-CF_3$ signal of racemic Mosher's carboxylate.

3. Conclusion

In conclusion, we have synthesized a new series of mono-ammonium CILs derived from isomannide, a carbohydrate-based biorenewable substrate. The effect of symmetry, molecular weight and charge delocalization of cations and anions on the melting points of these CILs has been demonstrated. The enantiomeric recognition ability of these CILs has been investigated by studying the diastereomeric interactions between CILs and racemic substrate probed by NMR spectroscopy. These observations indicate the potential of this new class of CILs in the resolution of racemates, as chiral shift reagents and as chiral solvents/catalysts in asymmetric synthesis. Further studies are in progress in our laboratory.

4. Experimental

Melting points were determined on a Thomas Hoover Capillary Melting Point instrument. The specific rotations were measured on AUTOPOL® IV automatic polarimeter from Rudolph Research Analytical. The ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer at 300 and at 75.5 MHz, respectively, using TMS as internal standard. The ^{19}F NMR spectra were recorded on a Bruker ARX-300 spectrometer at 282.4 MHz using hexafluorobenzene as reference. The chemical shift values are on δ scale and the coupling constants (J) are in Hertz. The high resolution mass spectra were done on a microTOF-Q instrument from Bruker Daltonics, Bermen and were recorded with ESI in positive mode. The X-ray crystallography was done on Bruker 2001 SAINT, SHELXTL, SMART, XCIF. Bruker AXS, Inc., Madison, Wisconsin, USA. All the chemicals used were purchased either from Aldrich Chemical Co. or Fluka Chemicals Co., USA and used without further purification. Analytical TLCs were performed on pre-coated Merck Silica Gel $60F_{254}$ plates; the spots were detected under UV light. Silica gel (100–200 mesh) was used for column chromatography.

4.1. Procedure for tosylation of D-isomannide

D-Isomannide **1** (50 g, 0.34 mol) was dissolved in dichloromethane (150 mL) in a round bottom flask followed by the addition of pyridine (55 mL). The reaction mixture was stirred in an ice-bath at 0–5 °C, followed by slow addition of *p*-toluenesulfonyl chloride (98 g, 0.51 mol). After the addition of *p*-toluenesulfonyl chloride, the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with some more dichloromethane (50 mL) and then washed with 1 M HCl (2 × 100 mL), water (100 mL), and brine (100 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was a mixture of compounds **9** and **10** which were separated and purified by silica gel column chromatography using chloroform/methanol as solvent system in increasing order of polarity.

4.1.1. (1*S*,4*R*,5*R*,8*R*)-8-(*p*-Toluenesulfonyloxy)-2,6-dioxabicyclo [3.3.0] octan-4-ol 9. This compound was obtained as a white solid, melting point 100–102 °C (lit. mp 102–104 °C)[22a] in 44% (45 g) yield. $[\alpha]_D^{22} = +95.3$ (*c* 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (3H, s, CH_3), 2.59 (1H, br s, OH), 3.54 (1H, dd, $J(H_{3a},H_{3b}) = 9.2$ Hz and $J(H_{3b},H_4) = 7.2$ Hz, H_{3b}), 3.78 (1H, dd, $J(H_{7a},H_{7b}) = 9.4$ Hz and $J(H_{7b},H_8) = 7.5$ Hz, H_{7b}), 3.93–4.04 (2H, m, H_{3a} and H_{7a}), 4.28 (1H, q, $J = 6.3$ Hz, H_4), 4.43 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 4.9$ Hz, H_5), 4.49 (1H, t, $J(H_1,H_5) = J(H_1,H_8) = 4.9$ Hz, H_1), 4.87–4.93 (1H, m, H_8), 7.36 (2H, d, $J = 8.4$ Hz, $H_{3'}$ and $H_{5'}$), 7.83 (2H, $J = 8.4$ Hz, $H_{2'}$ and $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.51 (CH_3), 68.89 (C-3), 71.17 (C-4), 72.77 (C-7), 77.31 (C-5), 78.89 (C-1), 80.28 (C-8), 126.83 (C-3′ and C-5′), 128.77 (C-2′ and C-6′), 131.91 (C-4′), 144.13 (C-1′); HRMS (ESI) *m/z* 323.0553 ($[M+Na]^+$, $C_{13}H_{16}O_6SNa$ calcd, 323.0565).

4.1.2. (1*S*,4*R*,5*S*,8*R*)-4,8-Bis(*p*-toluenesulfonyloxy)-2,6-dioxabicyclo [3.3.0] octane 10. This compound was obtained as a white solid with melting point 82–84 °C (lit. mp 89–90 °C)[29] in 28% (44 g) yield. $[\alpha]_D^{22} = +78.5$ (*c* 0.6, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (6H, s, 2 × CH_3), 3.72 (2H, dd, $J(H_{7a},H_{7b}) = J(H_{3a},H_{3b}) = 9.4$ Hz, $J(H_{7b},H_8) = J(H_{3b},H_4) = 7.6$ Hz, H_{3b} and H_{7b}), 3.90 (2H, dd, $J(H_{7a},H_{7b}) = J(H_{3a},H_{3b}) = 9.4$ Hz, $J(H_{7a},H_8) = J(H_{3a},H_4) = 6.6$ Hz, H_{3a} and H_{7a}), 4.45–4.47 (2H, m, $J(H_1,H_5) = J(H_1,H_8) = J(H_4,H_5) = 4.0$ Hz, H_1 and H_5), 4.80–4.87 (2H, m, H_4 and H_8), 7.34 (4H, d, $J = 8.1$ Hz, $H_{3'}$, $H_{3''}$, $H_{5'}$ and $H_{5''}$) and 7.80 (4H, d, $J = 8.1$ Hz, $H_{2'}$, $H_{2''}$, $H_{6'}$ and $H_{6''}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 20.49 (2 × CH_3), 68.91 (C-3 and C-7), 76.84 (C-1 and C-5), 78.80 (C-4 and C-8), 126.75 (C-3′, C3″, C-5′, and C-5″), 128.80 (C-2′, C2″, C-6′, and C-6″), 131.81 (C-4′ and C-4″) and 144.19 (C-1′ and C-1″); HRMS (ESI): *m/z* 477.0659 ($[M+Na]^+$, $C_{20}H_{22}O_8S_2Na$ calcd, 477.0654).

4.2. (1*S*,4*R*,5*R*,8*R*)-4-Ethoxy-8-(*p*-toluenesulfonyloxy)-2,6-dioxabicyclo [3.3.0] octane 11

Isomannide monotosylate **9** (39 g, 0.13 mol) was dissolved in dichloromethane (250 mL) in a round bottom flask, 50% aq KOH solution (30 mL) and tetrabutylammonium bromide (TBAB) (2 g) were added, followed by the addition of ethyl bromide (29.11 mL, 0.39 mol). The reaction mixture was then stirred at room temperature and the progress of the reaction was monitored on TLC using 30% ethyl acetate/hexanes as solvent system. After completion of the reaction in around 24 h, some more water was added to the reaction mixture (50 mL). The organic layer was separated and the aqueous layer was washed further with dichloromethane (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuum. The crude product was purified further by silica gel column chromatography using ethyl acetate/hexanes as a solvent system in increasing order of polarity to obtain compound **11** as a light yellow oil in 85% yield (36.24 g) from compound **2**. $[\alpha]_D^{22} = +91.4$ (*c* 0.85, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, t, $J = 7.0$ Hz, CH_3CH_2O), 2.44 (3H, s, CH_3), 3.45–3.70 (3H, m, H_{3b} and CH_3CH_2O), 3.80 (1H, dd, $J(H_{7a},H_{7b}) = 9.4$ Hz and $J(H_{7a},H_8) = 7.2$ Hz, H_{7b}), 3.90–4.02 (3H, m, H_{3a}, H_{7a} and H_4), 4.47 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 4.5$ Hz, H5), 4.52 (1H, t, $J(H_1,H_5) = J(H_1,H_8) = 4.5$ Hz, H_1), 4.84–4.91 (1H, m, H_8), 7.33 (2H, d, $J = 8.3$ Hz, $H_{3'}$ and $H_{5'}$), 7.81 (2H, $J = 8.3$ Hz, $H_{2'}$ and $H_{6'}$). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.68 (CH_3CH_2O), 22.03 (CH_3), 66.68 (CH_3CH_2O), 70.68 (C-3), 71.25 (C-7), 79.10 (C-4), 80.26 (C-5), 80.59(C-1), 80.63 (C-8), 128.33 (C-3′ and C-5′), 130.25 (C-2′ and C-6′), 133.70 (C-4′) and 145.51 (C-1′); HRMS (ESI): *m/z* 351.0862 ($[M+Na]^+$, $C_{15}H_{20}O_6SNa$ calcd, 351.0878).

4.3. (1*R*,4*R*,5*R*,8*S*)-4-Ethoxy-8-(benzylamino)-2,6-dioxabicyclo [3.3.0] octane 12

To compound **11** (27 g, 82.07 mmol) taken in a round bottom flask, benzylamine (80 mL) was added and the reaction mixture stirred at 180 °C under a nitrogen atmosphere for 12 h. After consumption of the starting material (on TLC), the reaction mixture was cooled to room temperature and excessive benzylamine was removed under reduced pressure and the residue dissolved in dichloromethane (150 mL). The white crystalline solid of tosylbenzylamine salt was filtered off and the filtrate was washed with water and then dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product still containing a slight amount of benzylamine and some complex mixture of non-polar impurities was purified by silica gel chromatography using 50% ethyl acetate/hexanes as solvent system in increasing order of polarity. The purified compound **12** was obtained as a light yellow oil in 60% (13 g). $[\alpha]_D^{22} = +94.0$ (*c* 1.076, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, t, $J = 6.9$ Hz, CH_3CH_2O), 1.56 (1H, br s, NH), 3.34–3.36 (1H, m, H_8), 3.48–3.81 (6H, m, CH_3CH_2O, $NHCH_2Ph$, H_{3a} and H_{3b}), 3.90–3.99 (2H, m, H_4 and H_{7b}), 4.05 (1H, dd, $J(H_{7a},H_{7b}) = 9.3$ Hz and $J(H_{7a},H_8) = 5.0$ Hz, H_{7a}), 4.45 (1H, br d, $J(H_1,H_5) = 4.3$ Hz, H_1), 4.60 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 4.3$ Hz, H_5), 7.23–7.35 (5H, m, aromatic H's); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.74 (CH_3CH_2O), 52.49 ($NHCH_2$-Ph), 65.44 (C-8), 66.49 (CH_3CH_2O), 70.17 (C-3), 74.56 (C-7), 80.51 (C-4), 80.55 (C-1), 88.15 (C-5), 127.55 (C-4′), 128.52 (C-3′ and C-5′), 128.87 (C-2′ and C-6′), and 140.08

(C-1′); HRMS (ESI): *m*/*z* 264.1587 ($[M+H]^+$, $C_{15}H_{22}NO_3$ calcd, 264.1600).

4.4. ((1*R*,4*R*,5*R*,8*S*)-4-Ethoxy-2,6-dioxabicyclo [3.3.0] octan-8-yl)-dimethylbenzylammonium iodide 13

The *sec*-amine **12** (15 g, 57.03 mmol) was dissolved in acetonitrile (150 mL) and anhydrous K_3CO_3 (1 equiv) was added, followed by the addition of methyl iodide (21 mL, 0.34 mol). The reaction mixture was then stirred at room temperature. After completion of the reaction (14 h), the K_2CO_3 was filtered off and the filtrate was concentrated under vacuum. The crude product was washed once with acetone to give the desired compound **13** as a white solid, mp = 170 °C in 83% (19.83 g) yield. $[\alpha]_D^{22} = +54.8$ (*c* 0.96, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, t, $J = 6.9$ Hz, CH_3CH_2O), 3.34 (3H, s, NCH_3), 3.46–3.71 (5H, m, NCH_3 and $CH_3\mathit{CH}_2O$), 3.76 (1H, dd, $J(H_{3a},H_{3b}) = 9.8$ and $J(H_{3a},H_4) = 4.4$ Hz, H_{3a}), 3.84 (1H, dd, $J(H_{3a},H_{3b}) = 9.8$ Hz and $J(H_{3b},H_4) = 5.0$ Hz, H_{3b}), 3.93–3.95 (1H, m, H_8), 4.02 (1H, q, $J = 4.9$ Hz, H_4), 4.28 (1H, dd, $J(H_{7a},H_{7b}) = 12.0$ Hz and $J(H_{7a},H_8) = 6.0$ Hz, H_{7a}), (1H, dd, $J(H_{7a},H_{7b}) = 12.0$ Hz and $J(H_{7b},H_8) = 2.0$ Hz, H_{7b}), 5.07 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 5.7$ Hz, H_5), 5.15 (1H, d, $J(H_x,H_y) = 13.0$ Hz, H_x), 5.24 (1H, d, $J(H_x,H_y) = 13.0$ Hz, H_y), 5.79 (1H, d, $J(H_1,H_5) = 5.7$ Hz, H_1), 7.40–7.47 (3H, m, $H_{3'}$, $H_{4'}$ and $H_{5'}$) and 7.72–7.75 (2H, m, $H_{2'}$ and $H_{6'}$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.76 ($\mathit{C}H_3CH_2O$), 49.61 and 49.96 ($2 \times N\mathit{C}H_3$), 66.89 ($\mathit{C}H_2Ph$), 67.80 ($CH_3\mathit{C}H_2O$), 68.67 (C-3), 72.23 (C-7), 78.00(C-8), 79.28 (C-4), 82.25 (C-5), 83.01 (C-1), 126.87 (C-4′), 129.67 (C-3′ and C-5′), 131.29 (C-2′ and C-6′), and 133.96 (C-1′); HRMS (ESI): *m*/*z* 292.1894 ($[M]^+$, $C_{17}H_{26}NO_3{}^+$ (the organic cationic moiety) calcd, 292.1913).

4.5. ((1*R*,4*R*,5*R*,8*S*)-4-Ethoxy-2,6-dioxabicyclo [3.3.0] octan-8-yl)-dimethylbenzylammonium bis(triflic)imide 14

To the iodide salt **13** (2 g, 4.8 mmol) in water (15 mL) in a RB flask at 60 °C (high temperature was needed because iodide salt **13** was not completely soluble in water at room temperature), lithium bis(triflic) amide (1.6 g, 5.7 mmol) was added and the reaction mixture was stirred for 6 h, after which the product separated as a highly viscous oil at the bottom of a round bottom flask. The water was decanted off and the residue was further washed with water (3 × 10 mL) when the desired compound **14** was obtained as a viscous oil in 85% (2.3 g) yield. $[\alpha]_D^{22} = +35.6$ (*c* 0.88, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, t, $J = 6.9$ Hz, $C\mathit{H}_3CH_2O$), 3.00 (3H, s, NCH_3), 3.07 (3H, s, NCH_3), 3.48–3.73 (2H, m, $CH_3C\mathit{H}_2O$), 3.76–3.86 (3H, m, H_{3a}, H_{3b} and H_8), 4.01 (1H, q, $J = 5.1$ Hz, H_4), 4.27–4.37 (2H, m, H_{7a} and H_{7b}), 4.48 (1H, d, $J(H_x,H_y) = 13.2$ Hz, H_x), 4.57 (1H, d, $J(H_x,H_y) = 13.2$ Hz, H_y), 4.87 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 5.7$ Hz, H_5), 5.12 (1H, d, $J(H_1,H_5) = 5.7$ Hz, H_1), 7.44–7.54 (5H, m, aromatic H's); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.59 ($\mathit{C}H_3CH_2O$), 49.93 and 50.35 ($2 \times N\mathit{C}H_3$), 67.86 ($\mathit{C}H_2Ph$), 68.90 ($CH_3\mathit{C}H_2O$), 70.02 (C-3), 72.98 (C-7), 79.17(C-8), 80.07 (C-4), 82.57 (C-5), 83.81 (C-1), 121.08 (q, $J = 321.2$, $(\mathit{C}F_3SO2)_2N$), 126.98 (C-4′), 130.87 (C-3′ and C-5′), 132.63 (C-1′), 134.44 (C-2′ and C-6′); ^{19}F NMR (282.4 MHz, acetone-d_6): δ −80.27 ($(\mathit{CF}_3\ SO_2)_2N^-$); HRMS (ESI): *m*/*z*292.1899 ($[M]^+$, $C_{17}H_{26}NO_3{}^+$ (the organic cationic moiety) calcd, 292.1913).

4.6. ((1*R*,4*R*,5*R*,8*S*)-4-Ethoxy-2,6-dioxabicyclo [3.3.0] octan-8-yl)-dimethylbenzylammonium hexafluorophosphate 15

To a solution of the iodide salt **13** (2 g, 4.8 mmol) in water (15 mL) at 50 °C, KPF_6 (1.1 g, 5.7 mmol) was added and the reaction mixture was stirred for 6 h. The product separated as a white solid, and then filtered, and washed twice with water to remove any remaining starting material. The desired compound **15** was obtained in 81% (1.7 g) yield, mp = 95 °C. $[\alpha]_D^{22} = +49.8$ (*c* 0.92, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, t, $J = 6.9$ Hz, $C\mathit{H}_3CH_2O$), 2.98 (3H, s, NCH_3), 3.07 (3H, s, NCH_3), 3.44–3.68 (2H, m, $CH_3C\mathit{H}_2O$), 3.72–3.82 (3H, m, H_{3a}, H_{3b}, and H_8), 3.97 (1H, q, $J = 4.9$ Hz, H_4), 4.23–4.36 (2H, m, H_{7a} and H_{7b}), 4.46 (1H, d, $J(H_x,H_y) = 13.4$ Hz, H_x), 4.56 (1H, d, $J(H_x,H_y) = 13.4$ Hz, H_y), 4.84 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 5.4$ Hz, H_5), 5.09 (1H, d, $J(H_1,H_5) = 5.4$ Hz, H_1), 7.43–7.49 (5H, m, aromatic H's); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 15.33 ($\mathit{C}H_3CH_2O$), 48.58 and 48.79 ($2 \times N\mathit{C}H_3$), 66.50 ($\mathit{C}H_2Ph$), 67.51 ($CH_3\mathit{C}H_2O$), 68.61 (C-3), 71.51 (C-7), 77.23 (C-8), 78.79 (C-4), 81.19 (C-5), 82.43 (C-1), 125.92 (C-4′), 129.52 (C-3′ and C-5′), 131.19 (C-1′), 133.16 (C-2′ and C-6′); ^{19}F NMR (282.4 MHz, CD_3CN): δ −75.38 ($PF_6{}^-$); HRMS (ESI): *m*/*z* 292.1897 ($[M]^+$, $C_{17}H_{26}NO_3{}^+$ (the organic cationic moiety) calcd, 292.1913).

4.7. ((1*R*,4*R*,5*R*,8*S*)-4-Ethoxy-2,6-dioxabicyclo [3.3.0] octan-8-yl)-dimethylbenzylammonium trifluoroacetate 16

To a solution of the iodide salt **13** (2 g, 4.8 mmol) in water (15 mL) at 50 °C, an aqueous solution of CF_3COOAg (1.06 g, 4.8 mmol in 3 mL water) was added. The yellow precipitate of AgI started forming, the reaction mixture was stirred for 30 min and the AgI precipitate was filtered off. A fresh solution of 1 M CF_3COOAg was added to the filtrate dropwise until the precipitation was completed, the last excessive drop of CF_3COOAg solution was neutralized by a drop of 1 M solution of iodide **13**. The AgI precipitate was again filtered off and the filtrate was concentrated under vacuum to remove water. The compound **16** was thus obtained as a colorless oil in 72.43% (1.4 g) yield. $[\alpha]_D^{22} = +53.1$ (*c* 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (3H, t, $J = 6.9$ Hz, $C\mathit{H}_3CH_2O$), 3.05 (3H, s, NCH_3), 3.13 (3H, s, NCH_3), 3.44–3.69 (2H, m, $CH_3C\mathit{H}_2O$), 3.76 (2H, ddd, $J(H_{3a},H_{3b}) = 9.6$ Hz, $J(H_{3a},H_4) = 4.9$ Hz and $J(H_{3b},H_4) = 5.1$ Hz, H_{3a} and H_{3b}), 3.85–3.91 (1H, m, H_8), 3.97 (1H, q, $J = 5.2$ Hz, H_4), 4.26 (1H, dd, $J(H_{7a},H_{7b}) = 11.9$ Hz and $J(H_{7a},H_8) = 6.1$ Hz, H_{7a}), 4.41 (1H, dd, $J(H_{7a},H_{7b}) = 11.9$ Hz and $J(H_{7b},H_8) = 3.0$ Hz, H_{7b}), 4.61 (1H, d, $J(H_x,H_y) = 13.0$ Hz, H_x), 4.69 (1H, d, $J(H_x,H_y) = 13.0$ Hz, H_y), 4.87 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 5.5$ Hz, H_5), 5.29 (1H, d, $J(H_1,H_5) = 5.5$ Hz, H_1), 7.34–7.56 (5H, m, aromatic H's); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.32 ($\mathit{C}H_3CH_2O$), 49.48 and 49.79 ($2 \times N\mathit{C}H_3$), 67.51 ($\mathit{C}H_2Ph$), 68.77 ($CH_3\mathit{C}H_2O$), 68.84 (C-3), 74.46 (C-7), 78.45 (C-8), 79.97 (C-4), 82.48 (C-5), 83.50 (C-1), 118.36 (q, $J = 296.5$, $\mathit{C}F_3$), 127.73 (C-4′), 130.30 (C-3′ and C-5′), 131.81 (C-1′), 134.39 (C-2′ and C-6′), and 162.10 (d, $J = 32.95$ Hz, $\mathit{C}OO^-$); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −79.75 ($C\mathit{F}_3COO^-$); HRMS (ESI): *m/z* 292.1897 ($[M]^+$, $C_{17}H_{26}NO_3^+$ (the organic cationic moiety) calcd, 292.1913).

4.8. ((1*R*,4*R*,5*R*,8*S*)-4-Ethoxy-2,6-dioxabicyclo [3.3.0] octan-8-yl)-dimethylbenzylammonium tetrafluoroborate 17

Tetrafluoroboric acid (purchased as a 48% solution in water) (5.76 mmol, 1.1 mL) was mixed with an aqueous suspension of silver oxide (667 mg, 2.88 mmol) in a conical flask covered with aluminum foil (silver oxide is light sensitive). The mixture was stirred until the solution became clear. The aqueous solution of silver tetrafluoroborate thus formed was mixed with the aqueous solution of mono-ammonium iodide **13** (2 g, 4.8 mmol) at 60 °C and the reaction mixture was stirred for 30 min. The silver iodide precipitate was filtered off and 1 M $AgBF_4$ solution was added to the filtrate dropwise to ensure total consumption of mono-ammonium iodide **6**. The last excess drop of $AgBF_4$ solution was neutralized by adding a drop of 1 M aqueous mono-ammonium iodide **13** solution. Finally, the AgI precipitate was filtered off and compound **17** crystallized out from the filtrate on cooling in ice bath as a white solid in 72.22% (1.3 g) yield, mp = 150 °C. $[\alpha]_D^{22} = +61.3$ (*c* 1, MeOH); ^1H NMR (300 MHz, CD_3CN): δ 1.17 (3H, t, $J = 7.0$ Hz, $C\mathit{H}_3CH_2O$), 2.93 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 3.49–3.74 (3H, m, H_{3b} and $CH_3C\mathit{H}_2O$), 3.84 (1H, dd, $J(H_{3a},H_{3b}) = 9.5$ Hz, $J(H_{3a},H_4) = 5.3$ Hz, H_{3a}), 3.92–3.96 (1H, m, H_8), 4.02 (1H, q, $J = 5.3$ Hz, H_4), 4.24 (1H, dd, $J(H_{7a},H_{7b}) =$ 11.9 Hz and $J(H_{7a},H_8) = 5.4$ Hz, H_{7a}), 4.37 (1H, dd, $J(H_{7a},H_{7b}) = 11.9$ Hz and $J(H_{7b},H_8) = 4.2$ Hz, H_{7b}), 4.48 (2H, s, $C\mathit{H}_2Ph$), 4.82 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 5.3$ Hz, H_5), 5.11 (1H, d, $J(H_1,H_5) = 5.3$ Hz, H_1), 7.49–7.60 (5H, m, aromatic H's); ^{13}C NMR (75.5 MHz, CD_3CN): δ 15.79 ($\mathit{C}H_3CH_2O$), 49.45 and 49.59 (2 × $N\mathit{C}H_3$), 66.97 ($\mathit{C}H_2Ph$), 68.53 ($CH_3\mathit{C}H_2O$), 68.59 (C-3), 72.10 (C-7), 79.73 (C-8), 79.77 (C-4), 82.39 (C-5), 83.11 (C-1), 127.75 (C-1′), 130.29 (C-3′ and C-5′), 131.96 (C-4′), 134.39 (C-2′ and C-6′); ^{19}F NMR (282.4 MHz, CD_3CN): δ −151.08 (BF_4^-); HRMS (ESI): *m/z* 292.1905 ($[M]^+$, $C_{17}H_{26}NO_3^+$ (the organic cationic moiety) calcd, 292.1913).

4.9. ((1*R*,4*R*,5*R*,8*S*)-4-Ethoxy-2,6-dioxabicyclo [3.3.0] octan-8-yl)-dimethylbenzylammonium trifluorosulfonate 18

Trifluoromethanesulfonic acid (0.52 mL, 5.8 mmol) was mixed with an aqueous suspension of silver oxide (667 mg, 2.88 mmol) in a conical flask covered with aluminum foil. The mixture was stirred until the solution became clear. The aqueous solution of silver trifluoromethanesulfonate thus formed was mixed with the aqueous solution of mono-ammonium iodide **13** (2 g, 4.8 mmol) at 60 °C and the reaction mixture was stirred for 30 min. The silver iodide precipitate was filtered off and 1 M CF_3SO_3Ag solution was added to the filtrate dropwise to ensure total consumption of mono-ammonium iodide **13**. The last excess drop of CF_3SO_3Ag solution was neutralized by adding a drop of 1 M aqueous mono-ammonium iodide **13** solution. The AgI precipitate was filtered off and the compound **18** was obtained by removing water under vacuum as a white solid in 76.2% (1.6 g) yield, mp = 80 °C. $[\alpha]_D^{22} = +60.5$ (*c* 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (3H, t, $J = 6.9$ Hz, $C\mathit{H}_3CH_2O$), 3.07 (3H, s, NCH_3), 3.15 (3H, s, NCH_3), 3.40–3.67 (2H, m, $CH_3C\mathit{H}_2O$), 3.71–3.85 (3H, m, H_{3a},H_{3b} and H_8), 3.98 (1H, q, $J = 4.9$ Hz, H_4), 4.26 (1H, dd, $J(H_{7a},H_{7b}) = 12.0$ Hz and $J(H_{7a},H_8) = 5.9$ Hz, H_{7a}), 4.40 (1H, dd, $J(H_{7a},H_{7b}) = 12.0$ Hz and $J(H_{7b},H_8) =$ 2.4 Hz, H_{7b}), 4.63 (1H, d, $J(H_x,H_y) = 13.1$ Hz, H_x), 4.72 (1H, d, $J(H_x,H_y) = 13.1$ Hz, H_y), 4.89 (1H, t, $J(H_1,H_5) = J(H_4,H_5) = 5.4$ Hz, H_5), 5.30 (1H, d, $J(H_1,H_5) = 5.4$ Hz, H_1), 7.42–7.56 (5H, m, aromatic H's); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.33 ($\mathit{C}H_3CH_2O$), 49.48 and 49.79 (2 × $N\mathit{C}H_3$), 67.48 ($\mathit{C}H_2Ph$), 68.74 ($CH_3\mathit{C}H_2O$), 69.03 (C-3), 72.44 (C-7), 78.71 (C-8), 79.90 (C-4), 82.39 (C-5), 83.44 (C-1), 121.66 (q, $J = 320.1$, $\mathit{C}F_3$), 127.32 (C-4′), 130.39 (C-3′ and C-5′), 132.13 (C-1′), 134.32 (C-2′ and C-6′); ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −79.21 ($C\mathit{F}_3SO_3^-$); HRMS (ESI): *m/z* 292.1900 ($[M]^+$, $C_{17}H_{26}NO_3^+$ (the organic cationic moiety) calcd, 292.1913).

4.10. ^{19}F NMR experiments

The racemic Mosher's silver salt (0.076 mmol, 26 mg) was mixed with a solution of CIL **13** (0.076 mmol, 32 mg) in 1 mL CD_3CN to exchange their anions at room temperature. The AgI precipitate thus formed was filtered off and the filtrate containing racemic Mosher's acid chiral ammonium salt **A** was transferred to NMR tube and subjected to ^{19}F NMR spectral recording without isolation. The same solution was mixed with CILs **13**–**18** (3.5 equiv) and again analyzed by ^{19}F NMR spectroscopy.

4.10.1. Effect of IL concentration. In different sets of experiments, the CD_3CN solution of Mosher's acid chiral ammonium salt **A** was mixed with different amounts of CIL **14** (2 equiv, 3.5 equiv, 7 equiv, and 10 equiv) and the effect of concentration of CIL was probed by ^{19}F NMR spectroscopy.

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