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Synthesis and Antimicrobial Activity of Imidazolium and Triazolium Chiral Ionic Liquids

Paweł Borowiecki,*[a] Małgorzata Milner-Krawczyk,[a] Dominika Brzezińska,[a] Monika Wielechowska,[a] and Jan Plenkiewicz[a]

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A simple and efficient procedure for the synthesis of new optically active imidazolium and triazolium ionic liquids in a three step reaction sequence is described. In the first step, the ring opening of 1,2-butylene oxide by imidazole or 1,2,4-triazole resulted in the formation of *N*-2-hydroxybutylimidazole and *N*-2-hydroxybutyl-1,2,4-triazole, respectively. In the second step, racemic mixtures of the secondary alcohols were resolved with good enantioselectivity by a lipase-catalyzed transesterification with enol esters (vinyl acetate and 1-acetoxy-2-methylcyclohexene). In the final step, the optically active intermediates were alkylated with several haloalkanes to yield optically active ionic liquids. The inhibitory activity of the synthesized ionic liquids was tested towards gram-negative and gram-positive bacteria and fungi.

Introduction

Ionic liquids (ILs) are salts consisting of an organic cation and an organic or inorganic anion with melting points near ambient temperature (below 100 °C).[1] The existing range of cation–anion combinations gives many possibilities for modification of the structure of the IL, which results in their diverse chemical and physical properties. Ionic liquids are often called "designer compounds", as their physical properties such as melting point, viscosity, density, and hydrophobicity can be modified by altering the nature of their cations and anions. ILs have attracted significant consideration as environmentally friendly media for electrochemistry,[2] chemical engineering, materials science, and especially for organic synthesis.[3] The last one is evolutional because the properties of the IL can be tuned according to the desired reactions. Thus, comprehensive studies of commonly named task-specific ILs with controllable and functionalized physical and chemical properties have recently been carried out. Chiral ionic liquids (CILs) are particularly interesting owing to their attractive applications for asymmetric synthesis,[4] stereoselective polymerization,[5] chiral gas chromatography,[6] NMR shift reagents,[7] and chiral liquid crystals.[8] The use of ILs in so called "green chemistry", for example, as media for chemical engineering, organic synthesis, or a replacement for many hazardous and volatile organic solvents raises questions about the toxicity of newly designed compounds. Therefore, it is crucial to select an IL that combines low toxicity with good chemical properties for use in industrial processes.[9] Moreover, recent studies have demonstrated the potential of certain ionic liquids to exhibit excellent antimicrobial activity, which raises the possibility that ionic liquids could find application as biocidal agents in the control of the growth of microorganisms.[10]

Nowadays, most CILs are prepared from naturally existing building blocks such as amino acids,[11] alkaloids,[12] sugars,[13] hydroxy acids,[14] and other precursors from the so-called chiral pool. Such an approach has many advantages because these compounds are usually available in a great amount and at low cost. On the other hand, it has disadvantages such as a limited number of available structures. For this reason, chiral imidazolium and especially triazolium ionic liquids containing one asymmetric carbon atom on the side of the cation with free hydroxy function were synthesized by an enzyme-catalyzed kinetic resolution by two teams of researchers in 2011.[15] The chiral ILs may be exploited in asymmetric synthesis as solvent and catalyst in one to accelerate catalytic reactions. Also, the unknown biological activity of these compounds is compelling, because the optically active secondary imidazolium alcohol (*S*)-(+)-**5a** can serve as a key intermediate in the synthesis of inhibitors of Ras farnesyl protein transferase (FPT).[16] In turn, its acetyl ester (*R*)-(+)-**6a** is a QC-36 molecule that exhibits anti-*Plasmodium* activity and is extremely important in malaria treatment.[17]

The ionic liquid field is dominated by imidazolium salts. There are very few triazolium derivatives that can be characterized as ionic liquids. Furthermore, until recently there was a lack of chiral triazolium quaternary salts of the type

[a] Warsaw University of Technology, Faculty of Chemistry, Noakowskiego St. 3, 00-664 Warsaw, Poland
Fax: +48-22-628-27-41
E-mail: pawel_borowiecki@onet.eu
pborowiecki@ch.pw.edu.pl
Homepage: http://www.ch.pw.edu.pl/
http://ztibsl.ch.pw.edu.pl/

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prepared by us with melting points < 100 °C. Moreover, the toxicity of the newly designed compounds has been verified against a panel of microorganisms including gram-negative and gram-positive bacteria and fungi.

Results and Discussion

Synthesis and Enzymatic Resolution of the *N*-2-(Hydroxybutyl)azoles

We report useful and straightforward syntheses of several optically active, liquid at room temperature quaternary imidazolium and triazolium salts. This new group of chiral ionic liquids has been prepared in a three step reaction sequence as presented in Scheme 1.

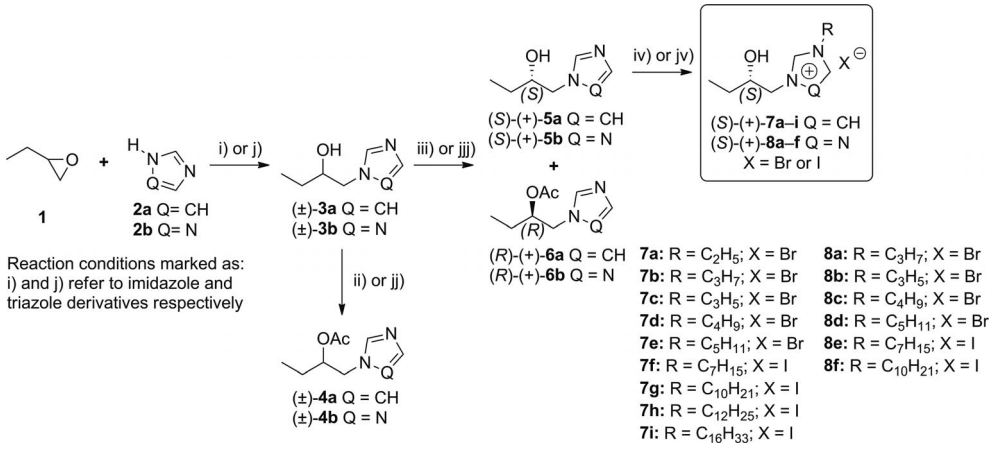
The first step of the process is based on solvent-free regioselective ring opening[18] of 1,2-butylene oxide (**1**) with imidazole (**2a**) or 1,2,4-triazole (**2b**). The neat reactions gave (±)-*trans*-1-(1*H*-imidazol-1-yl)butan-2-ol [(±)-**3a**] and (±)-*trans*-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol [(±)-**3b**] in yields ranging from 77 to 99% depending on the conditions applied (Table 1).

Table 1. Ring opening of 1,2-butylene oxide (**1**) with imidazole (**2a**) or 1,2,4-triazole (**2b**) under solvent-free conditions.

Entry	Product	Equiv. of epoxide	Time [h]	*T* [°C]	Yield [%][a]
1	(±)-**3a**	1	12	60	82
2	(±)-**3a**	1	24	45	77
3	(±)-**3a**	1	72	60	99
4	(±)-**3b**	1.2	24	70	96

[a] Isolated yield.

The second step is the lipase-mediated kinetic resolution of the racemic alcohols (±)-**3a** and (±)-**3b**. Preliminary studies of this reaction were performed with (±)-**3a**. The main difficulty was the vigorous course of the reaction, which does not change even after modification of the conditions (significant dilution, reduction of enzyme and vinyl acetate quantity, or even cooling). A detailed examination of the reaction revealed that vinyl, isopropenyl, ethyl, and butyl acetates are too reactive with the investigated alcohol and react spontaneously even at low temperature without any catalyst. On the other hand, when 4-nitrophenyl butyrate was used as the acylating agent, neither spontaneous nor lipase-catalyzed reaction was observed. After these experiments, we decided to check if some other bulky acetate could terminate this undesirable hyperreactivity of the simple acetates. 1-Acetoxy-2-methylcyclohexene (**9**) was chosen, as it is highly sterically hindered and can be easily prepared from racemic 2-methylcyclohexanone by reaction with acetic anhydride and a catalytic amount of perchloric acid.[19] Finally, it turned out that its low reactivity prevents a spontaneous transesterification and simultaneously works as intended as an acyl donor in the lipase-catalyzed reaction. The next problem to be solved was the solvent selection. From several examined solvents that are commonly used in enzymatic reactions, we chose *tert*-amyl alcohol (2-methylbutan-2-ol), in which the resolution of (±)-**3a** was most effective (Table 2). After screening a few commercial lipases (Table 2, Entries 1–4), we noticed that room-temperature reactions with immobilized lipases (Novozym 435, Amano PS-C) were much faster than those with native enzymes (Amano AK, Amano PS). Nevertheless, it appeared that the reactions were significantly better catalyzed by the native enzymes, which led to a substantial increase in enantioselectivity (Table 2, Entries 2 and 3). The next two experiments (Table 2, Entries 5 and 6) were performed with Amano PS-IM lipase under modified conditions. We decreased the quantity of lipase and extend the reaction time to 52% substrate conversion (Table 2, Entry 6). As a result, the unreacted alcohol (+)-**5a** was obtained in high enantiomeric excess (*ee* = 98%). To achieve the opposite enantiomeric form of 1-(1*H*-imidazol-1-yl)butan-2-ol [(+)-**6a**] with high optical purity, the reaction was stopped at close to 45% conversion (*ee* = 99%, Table 2, Entry 7).



Scheme 1. Synthesis of optically active ILs. Reagents and conditions: (i) epoxide (1 equiv.), 60 °C, 72 h; (j) epoxide (1.2 equiv.), 70 °C, 24 h; (ii) Ac_2O (1.05 equiv.), DMAP (0.33 equiv.), pyridine (14 equiv.), neat, room temp., 72 h; (jj) vinyl acetate (5 equiv.), enzyme, 2-methyl-2-butanol, room temp.; (iii) 1-acetoxy-2-methylcyclohexene (2.5 equiv.), enzyme, 2-methyl-2-butanol, room temp., 250 rpm; (jjj) vinyl acetate (5 equiv.) or 1-acetoxy-2-methylcyclohexene (2.5 equiv.), enzyme, 2-methyl-2-butanol, room temp., 250 rpm; (iv) and (jv) RX (3 equiv.), Δ, dry CH_3CN.

Table 2. Lipase-catalyzed resolution of (±)-**3a**.

Entry	Enzyme	*t* [h]	Conv.[e] [%]	Product	*ee*[f] [%]	*E*[g]	Yield[h] [%]
1	Novozym 435[a]	94	46	alcohol	71	19	98
				ester	82		70
2	Amano PS[a]	163	41	alcohol	66	48	53
				ester	92		31
3	Amano AK[a]	163	43	alcohol	73	60	60
				ester	93		39
4	Amano PS-C[a]	49	42	alcohol	60	19	74
				ester	82		56
5	Amano PS-IM[b]	16	45	alcohol	72	17	80
				ester	87		72
6	Amano PS-IM[b]	18	52	alcohol	98	40	88
				ester	80		91
7	Amano PS-IM[c]	28	45	alcohol	82	>200	93
				ester	99		60
8	Amano PS-IM[d]	40	40	alcohol	64	53	70
				ester	93		75

[a] Conditions: (±)-**3a** 100 mg, lipase 100 mg, solvent 7.5 mL, acetylating agent 550 mg (5 equiv.). [b] Conditions: (±)-**3a** 1 g, lipase 0.3 g, solvent 10 mL, acetylating agent 2.2 g (2 equiv.). [c] Conditions: (±)-**3a** 1 g, lipase 0.3 g, solvent 10 mL, acetylating agent 1.65 g (1.5 equiv.). [d] Conditions: (±)-**3a** 2 g, lipase 0.3 g, solvent 20 mL, acetylating agent 2.64 g (1.2 equiv.). [e] Based on GC, for confirmation the % conversion was calculated from the enantiomeric excess of the starting material (ee_s) and the product (ee_p) according to the formula: conv. = $ee_s/(ee_s + ee_p)$. [f] Determined by HPLC analysis with a Chiralcel OD-H column. [g] $E = \ln[(1 - \text{conv.})(1 - ee_s)]/\ln[(1 - \text{conv.})(1 + ee_s)]$.

As we had confirmed that the problem of spontaneous transesterification of racemic (±)-**3b** by vinyl acetate does not exist, we screened three lipase preparations as catalysts of the reaction with enol esters (vinyl acetate or 1-acetoxy-2-methylcyclohexene in 2-methyl-2-butanol, Table 3) to find the most efficient system. The lipase-catalyzed transesterification reaction with vinyl acetate as acyl donor, proceeded faster than the reaction with 1-acetoxy-2-methylcyclohexene (Table 3, Entries 6 and 7). All of the lipase-catalyzed kinetic resolutions of racemic (±)-**3b** yielded enantiomerically enriched products with satisfactory *ee* values that ranged from 89 to 100% for (*S*)-(+)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol [(+)-**5b**] and from 92 to 98% for (*R*)-(+)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl acetate [(+)-**6b**].

The racemic acetates (±)-**4a** and (±)-**4b** were required for the determination of the purity of the separated enantiomerically enriched acetates. The acetate (±)-**4a** was prepared by a classical procedure with acetic anhydride, pyridine, and 2-dimethylaminopyridine (DMAP), but (±)-**4b** was prepared in a lipase-catalyzed reaction because a conventional esterification of the alcohol (±)-**3b** gives many side products, which lowers the overall yield to ca. 30%. Therefore, we decided to use the enzyme-catalyzed reaction instead of the standard one and to stop it at the very latest possible stage to achieve almost 100% conversion of alcohol to ester. In this way, we obtained the desired racemic 1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl acetate [(±)-**4b**] with a very acceptable yield (91%, Table 4).

Table 4. Synthesis of acetylated standard samples (±)-**4a** and (±)-**4b** for enzymatic reactions.

Entry	Product	Acylating agent	Solvent	Catalyst	Time [h]	Yield [%][a]
1	(±)-**4a**	Ac_2O	–	pyridine + DMAP	72	64
2	(±)-**4b**	vinyl acetate	2-methyl-2-butanol	Novozym SP 435	48	91

[a] Isolated yield.

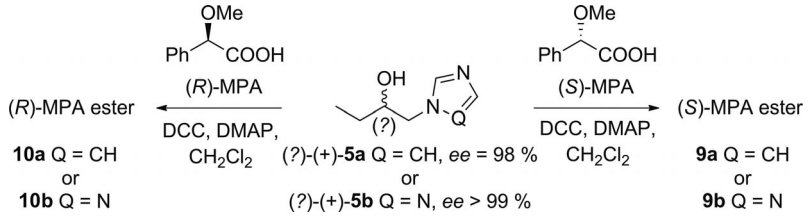
Stereochemistry Determination of Alcohols (+)-5a and (+)-5b

The stereochemical preference of the PS-IM lipase in the acetylation reaction of (±)-**3a** and (±)-**3b** can be determined by establishing the absolute configuration of the chiral center in the slower reacting enantiomer of imidazolic alcohol (+)-**5a** and triazolic alcohol (+)-**5b**. For these alcohols, a simple ^{1}H NMR method based on double derivatization described by Mosher[20] can be applied. We achieved this by transformation of the investigated alcohol enantiomer [(+)-**5a** or (+)-**5b**] into two diastereomeric esters

Table 3. Lipase-catalyzed resolution of (±)-**3b**.

Entry	Enzyme	Acylating agent	*t* [h]	*T* [°C]	Conv.[c] [%]	Product	*ee*[d] [%]	*E*[e]	Yield[f] [%]
1	Amano PS[a]	vinyl acetate	108	r.t.	49	alcohol	89	83	64
						ester	93		56
2	Amano AK[a]	vinyl acetate	18	r.t.	51	alcohol	96	>100	68
						ester	92		60
3	Amano PS-IM[a]	vinyl acetate	17	r.t.	52	alcohol	> 99	>200	58
						ester	94		53
4	Amano PS-IM[b]	1-acetoxy-2-methylcyclohexene	17	r.t.	51	alcohol	> 99	>200	61
						ester	95		57
5	Amano PS-IM[a]	vinyl acetate	5	30	48	alcohol	92	>200	92
						ester	98		77
6	Amano PS-IM[a]	vinyl acetate	6	30	50	alcohol	98	>200	75
						ester	97		66
7	Amano PS-IM[b]	1-acetoxy-2-methylcyclohexene	9	30	49	alcohol	92	91	84
						ester	93		86

[a] Conditions: (±)-**3b** 1 g, lipase 0.3 g, solvent 10 mL, vinyl acetate 3 g (5 equiv.). [b] Conditions: (±)-**3b** 1 g, lipase 0.3 g, solvent 5 mL, 1-Acetoxy-2-methylcyclohexene 2.73 g (2.5 equiv.). [c] Based on GC, for confirmation the % conversion was calculated from the enantiomeric excess of the starting material (ee_s) and the product (ee_p) according to the formula: conv. = $ee_s/(ee_s + ee_p)$. [d] Determined by HPLC analysis with a Chiralcel OD-H column. [e] $E = \ln[(1 - \text{conv.})(1 - ee_s)]/\ln[(1 - \text{conv.})(1 + ee_s)]$. [f] Isolated yield after column chromatography.



Scheme 2. Assignment of the absolute configuration of alcohols (+)-**5a** and (+)-**5b**.

$$\textbf{(+)-5a}\begin{cases}\Delta\delta^{RS}L_1 = \delta L_1(R) - \delta L_1(S) = 7.36 - 6.37 = 0.99 > 0\\ \Delta\delta^{RS}L_2 = \delta L_2(R) - \delta L_2(S) = 0.64 - 0.86 = -0.22 < 0\end{cases}$$

$$\textbf{(+)-5b}\begin{cases}\Delta\delta^{RS}L_1 = \delta L_1(R) - \delta L_1(S) = 7.86 - 7.11 = 0.75 > 0\\ \Delta\delta^{RS}L_2 = \delta L_2(R) - \delta L_2(S) = 0.70 - 0.91 = -0.21 < 0\end{cases}$$

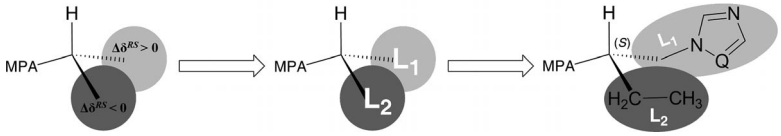


Figure 1. Description of substituents for determination of the absolute configuration of (+)-**5a** and (+)-**5b**.

by reacting it separately with chiral auxiliary [(*R*)- and (*S*)-α-methoxy-α-phenylacetic acid (MPA), Scheme 2], followed by comparison of the ^{1}H NMR spectra of the resulting two derivatives of each enantiomer of the alcohol (Figure 2).

Taking into consideration the finding[21] that in the α-methoxy-α-phenylacetic acid esters of secondary alcohols, the most representative and energetically favorable (stable) is the sp conformer, and evaluating differences in chemical shifts of the relevant protons in the MPA-esters, the absolute configuration of the investigated enantiomeric form of both alcohols has been assigned as (*S*).

The results of the equations presented in Figure 1 and an examination of the ^{1}H NMR spectroscopic data of the (*R*)- and (*S*)-MPA ester derivatives are consistent with the three-dimensional structure proposed in Figure 2.

It is easily noticed that if the absolute configuration of the slower reacting enantiomer of (+)-**5a** or (+)-**5b** is (*S*), the substituents are arranged in such a way that in the (*S*)-MPA esters, the imidazole ring H(2′) and triazole ring H(5′) protons are shielded by the phenyl ring (owing to the space-orientated anisotropic effect), whereas the same protons in the (*R*)-MPA esters are unaffected. An especially big difference (δ = 0.99 ppm) of the H(2′) proton chemical shifts in both MPA esters of imidazolium derivatives **10a** and **9b** is observed. The opposite effect is found for the aliphatic protons H(9′), which are shielded in (*R*)-MPA derivatives but remain unaffected in (*S*)-MPA. In the course of our study, it was observed that the lipase-catalyzed kinetic resolution of (±)-**3a** and (±)-**3b** fits the Kazlauskas rule,[22] and the (*R*)-ester and (*S*)-alcohol enantiomers are obtained.

Synthesis of Chiral Ionic Liquids

The alkylations of optically active (*S*)-(+)-1-(1*H*-imidazol-1-yl)butan-2-ol (+)-**5a** or (*S*)-(+)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (+)-**5b** were carried out with a few bromo- or iodoalkanes. The haloalkane was added in excess to a solution of (+)-**5a** or (+)-**5b** in acetonitrile previously dried with molecular sieves (4 Å). The quaternization of the N-3 atom of imidazole and the N-4 atom of the 1,2,4-triazole ring of the derivatives produced salts (+)-**7a**–**i** and (+)-**8a**–**f** in > 75% and > 49% isolated yields, respectively (Table 5). We noticed that product (+)-**7a** could only be obtained successfully in a pressurized reactor because ethyl bromide presents serious problems of low reactivity and volatility. All except one of the prepared imidazolium quaternary salts are liquid at room temperature. On the other hand, the triazolium salts are solids or very viscous liquids (gums).

Table 5. Synthesis of chiral imidazolium [(+)-**7a**–**i**] and triazolium [(+)-**8a**–**f**] ILs.

Entry	IL	R	X	*t* [h]	*T* [°C]	Yield [%]	M.p. [°C]	$[\alpha]_D^{29}$[b]
1	(+)-**7a**[a]	C_2H_5	Br	24	82	99	oil	+16.1
2	(+)-**7b**	C_3H_7	Br	96	65	99	oil	+15.2
3	(+)-**7c**	C_3H_5	Br	96	65	95	oil	+14.3
4	(+)-**7d**	C_4H_9	Br	96	80	94	oil	+12.7
5	(+)-**7e**	C_5H_{11}	Br	96	82	94	oil	+17.3
6	(+)-**7f**	C_7H_{15}	I	96	82	96	oil	+17.8
7	(+)-**7g**	$C_{10}H_{21}$	I	96	82	91	oil	+18.2
8	(+)-**7h**	$C_{12}H_{25}$	I	96	120	88	oil	+16.4
9	(+)-**7i**	$C_{16}H_{33}$	I	96	120	75	gum	+15.9
10	(+)-**8a**	C_3H_7	Br	48	65	87	gum	+12.3
11	(+)-**8b**	C_3H_5	Br	48	65	93	gum	+11.8
12	(+)-**8c**	C_4H_9	Br	48	80	49	89–90	+ 9.7
13	(+)-**8d**	C_5H_{11}	Br	48	82	98	gum	+13.4
14	(+)-**8e**	C_7H_{15}	I	48	82	90	81–83	+13.2
15	(+)-**8f**	$C_{10}H_{21}$	I	48	82	77	gum	+12.5

[a] Reaction was performed in pressure reactor. [b] Specific rotation; solution in chloroform (*c* 1.0).

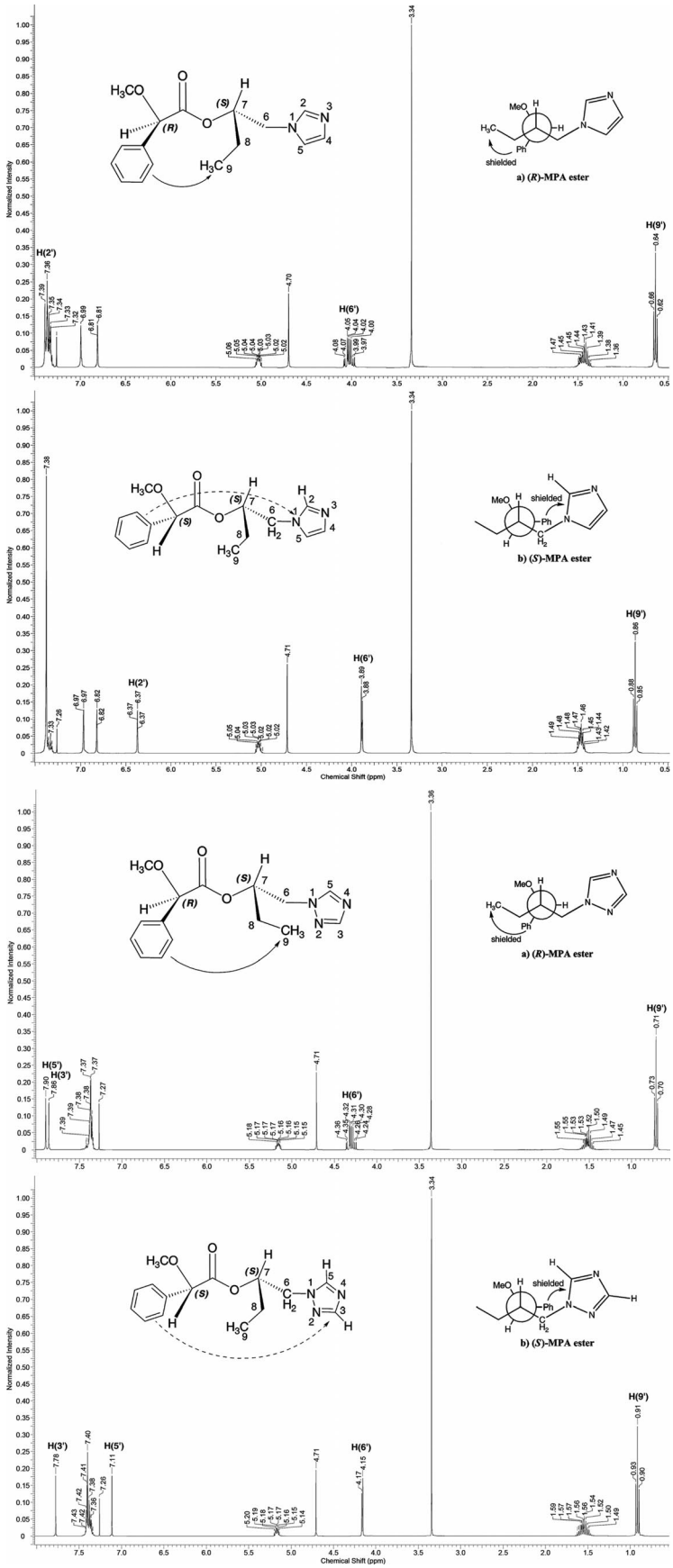


Figure 2. The assignment of the absolute configuration of the slower reacting enantiomers (+)-**5a** (the upper two spectra) and (+)-**5b** (the lower two spectra) by ^{1}H NMR spectra and $\Delta\delta^{RS}$ values of the (*R*)- and (*S*)-MPA esters.

Table 6. Growth inhibition halo [cm] for the racemic imidazolium and triazolium ILs (25 mM).

IL	R	*E. coli* ATCC 8739 G(–)	*S. typhimurium* ATCC 14028 G(–)	*P. aeruginosa* ATCC 9027 G(–)	*B. subtilis* ATCC 6633 G(+)	*S. aureus* ATCC 6538 G(+)	*C. albicans* ATCC 10231 yeast
(±)-**7b**	C_3H_7	–[a]	–	–	–	–	–
(±)-**7e**	C_5H_{11}	–	–	–	–	–	–
(±)-**7f**	C_7H_{15}	1.20 ± 0.00	1.08 ± 0.15	0.98 ± 0.04	1.15 ± 0.00	1.95 ± 0.07	1.13 ± 0.04
(±)-**7g**	$C_{10}H_{21}$	1.15 ± 0.07	–	1.15 ± 0.07	1.85 ± 0.07	2.00 ± 0.14	1.40 ± 0.00
(±)-**8a**	C_3H_7	–	–	–	–	–	–
(±)-**8d**	C_5H_{11}	–	–	–	–	–	–
(±)-**8e**	C_7H_{15}	1.15 ± 0.00	–	–	–	–	–
(±)-**8f**	$C_{10}H_{21}$	1.20 ± 0.00	1.15 ± 0.00	1.05 ± 0.00	1.58 ± 0.04	1.40 ± 0.00	1.20 ± 0.00

[a] –: no inhibition.

Table 7. The MIC (mM) values for the racemic imidazolium and triazolium ILs.

IL	R	*E. coli* ATCC 8739 G(–)	*S. typhimurium* ATCC 14028 G(–)	*P. aeruginosa* ATCC 9027 G(–)	*B. subtilis* ATCC 6633 G(+)	*S. aureus* ATCC 6538 G(+)	*C. albicans* ATCC 10231 yeast
(±)-**7g**	$C_{10}H_{21}$	0.4	0.5	2.1	0.5	0.4	0.2
(±)-**7h**	$C_{12}H_{25}$	0.08	0.3	1.1	0.3	0.005	0.3
(±)-**7i**	$C_{16}H_{33}$	0.4	0.8	3.8	0.5	0.3	2.7
(±)-**8f**	$C_{10}H_{21}$	1.3	3.3	4.4	3.4	0.6	1.0

Table 8. Antifungal activity (% of control) of the racemic imidazolium and triazolium ILs (1 mM).

IL	R	*F. oxysporum* MF 5	*F. sambucinum* MF 1	*F. culmorum* MF 18	*A. brasiliensis* ATCC 16404	*C. coccodis* MC 1	*P. infestans* MP 324	*P. infestans* MP 1320
(±)-**7b**	C_3H_7	94.12 ± 3.91	101.14 ± 3.62	100.40 ± 0.00	98.44 ± 3.21	93.91 ± 6.02	109.29 ± 5.26	104.32 ± 10.88
(±)-**7e**	C_5H_{11}	94.65 ± 6.09	93.51 ± 3.61	99.12 ± 2.64	89.96 ± 3.95	94.24 ± 3.65	105.05 ± 9.16	91.41 ± 2.85
(±)-**7f**	C_7H_{15}	32.99 ± 1.71	32.13 ± 2.54	55.42 ± 3.08	83.95 ± 2.85	86.55 ± 3.89	83.85 ± 1.51	45.95 ± 4.69
(±)-**7g**	$C_{10}H_{21}$	64.12 ± 3.90	53.82 ± 19.46	46.71 ± 2.28	78.93 ± 2.79	67.98 ± 3.00	86.22 ± 5.51	54.55 ± 1.75
(±)-**7h**	$C_{12}H_{25}$	24.54 ± 1.36	25.39 ± 0.78	40.21 ± 2.39	38.94 ± 15.96	52.16 ± 1.01	32.21 ± 27.90	62.86 ± 3.48
(±)-**7i**	$C_{16}H_{33}$	40.89 ± 2.58	33.59 ± 0.90	60.14 ± 7.57	27.63 ± 0.72	54.90 ± 4.44	44.11 ± 13.79	58.43 ± 13.70
(±)-**8a**	C_3H_7	93.77 ± 1.33	104.56 ± 1.92	101.21 ± 0.93	100.78 ± 0.78	99.57 ± 3.29	90.51 ± 3.76	108.39 ± 2.95
(±)-**8d**	C_5H_{11}	90.12 ± 3.39	95.42 ± 4.41	99.56 ± 2.27	89.12 ± 1.60	93.83 ± 1.90	105.05 ± 2.47	94.29 ± 20.89
(±)-**8e**	C_7H_{15}	87.76 ± 5.03	92.37 ± 3.82	93.17 ± 1.31	94.03 ± 1.04	95.09 ± 1.82	105.38 ± 1.45	81.15 ± 0.74
(±)-**8f**	$C_{10}H_{21}$	53.73 ± 4.75	24.12 ± 2.04	48.03 ± 0.76	91.19 ± 3.63	78.95 ± 0.00	69.29 ± 0.00	53.41 ± 3.12

Antimicrobial Activity of Ionic Liquids

The antimicrobial and antifungal activities of the synthesized ILs were evaluated against a wide range of microorganisms. The studies were conducted on three strains of gram-negative bacteria, two strains of gram-positive bacteria, and eight strains of fungi. For the bacteria and yeasts, we used an agar diffusion test as a preliminary screening method (Table 6), which allowed us to select the most promising compounds for further determination of minimal inhibitory concentrations (MICs) by a broth dilution method (Table 7). The antifungal activity was tested by an agar dilution method, and the results are listed in Table 8.

Some of the tested compounds exhibited quite strong activity and wide antibacterial and antifungal action. Their activity was greatly related to the alkyl chain length, which is in good agreement with observations made by numerous studies.[23] The strongest activity was observed in the case of imidazolium ILs with an alkyl chain substituent of 12 carbon atoms (Table 7). Moreover, the antibacterial activity of imidazolium ILs seems to be slightly stronger than activity of triazolium ILs (Tables 6 and 7). The relationship between alkyl chain length and antifungal activity of the tested compounds was less evident, however it could still be observed (Table 8), which is in keeping with observations made recently for other filamentous fungi.[24] Notably, the common feature of the ILs is a dependency of antimicrobial potency on the length of the carbon substituent, which suggests a general mechanism of action by membrane damage controlled by the lipophilicity of the cation (i.e., alkyl chain length).[25]

Conclusions

Lipase-catalyzed transesterification was established as an efficient technique for the kinetic resolution of secondary alcohols with an imidazole or 1,2,4-triazole ring. The enantiomerically enriched alcohols obtained by this method have proven to be valuable synthons for various optically

active room temperature ionic liquids. Interesting observations were made during the experiments of lipase-catalyzed acetylation of the racemic alcohol (±)-**3a**. We discovered some unexpected difficulties connected with a spontaneous transesterification of the alcohol by several acetates. The observations enabled us to suggest a hypothesis that a unique autocatalysis mechanism exists, which may be connected to the imidazolium ring of the substrate molecule. This problem has not been sufficiently considered and still lacks theoretical explanation although the lipase-catalyzed separation of the desired alcohol was effectively achieved by using a nonstandard acylating agent (1-acetoxy-2-methylcyclohexene). The antibacterial and antifungal activity of the final imidazolium and triazolium salts was evaluated by three different methods. Some of the tested compounds exhibited quite strong biological activity, which was greatly related to the alkyl chain length. Notably, the imidazolium salts revealed slightly stronger antibacterial activity than the triazolium salts.

Experimental Section

General Details: All commercially available reagents (Aldrich, Fluka and POCH) were used without further purification. Novozym SP 435 (lipase from *Candida antarctica B* immobilized on a macroporous acrylic resin, 10000 U/g), Amano PS (native lipase from *Burkholderia cepacia* earlier *Pseudomonas cepacia*, > 23.000 U/g), Amano PS-C (immobilized on ceramic particles), Amano PS-IM (immobilized on diatomite, 500 U/g), and Amano AK (native lipase from *Pseudomonas fluorescens*, 20.000 U/g) were purchased from Novo Nordisk Co. and Amano Pharmaceutical Co. and were used without any treatment. Melting points were obtained with an MPA100 Optimelt SRS apparatus. Thin-layer chromatography was performed with aluminum TLC plates with Kieselgel 60 F_{254} silica gel (Merck, 0.2 mm thickness film), and the compounds were visualized in iodine vapor. Preparative plate chromatography was performed with PSC-Fertigplatten Kieselgel 60 F_{254} (20 × 20 cm with 2 mm thickness layer). The chromatographic analyses (GLC) were performed with an HP Series II 5890 instrument equipped with a flame ionization detector (FID) and fitted with an HP-50+ (30 m) semipolar column. Helium (2 mL/min) was used as carrier gas; $T_{injector}$ = 280 °C, T_{column} = 100 °C (3 min) and 100–280 °C (10 °C/min); retention times (t_R) are given in minutes under these conditions. Column chromatography was performed with Silica gel 60 (Merck) of 40–63 μm. A mixture of chloroform/methanol was used as eluent (95:5, 9:1 or 8:2 v/v depending on substance purified). The enantiomeric excesses of the resulting esters and alcohols were determined by HPLC analysis with a Shimadzu CTO-10ASV chromatograph equipped with an STD-20A UV detector and a Chiralcel OD-H (Diacel) chiral column with mixtures of *n*-hexane/isopropyl alcohol as mobile phase in appropriate ratios given in experimental section; flow (*f*) is given in mL/min; racemic alcohols and esters were used as standards. Optical rotations were measured with a P20 polarimeter (Belligham & Stanley Ltd., line D spectrum of sodium) in a 2 dm long cuvette. UV spectra were measured with a Cary 3 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Varian Mercury 400BB spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei; chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard; signal multiplicity assignment: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; coupling constants (*J*) are given in Hertz (Hz). Mass spectra were recorded with a Micro-mass ESI Q-TOF spectrometer at the Mass Spectrometry Laboratory, Institute of Biochemistry and Biophysics (IBB), PAN. IR spectra were measured with a SPECORD M80 spectrometer. Samples were prepared in nujol. Elemental analyses were performed with a VARIO EL III (Elementar Analysensysteme GmbH) elemental analyzer.

Preparation of Racemic Alcohols and Esters for Kinetic Enzymatic Resolution

1-(1*H*-Imidazol-1-yl)butan-2-ol [(±)-3a]: A mixture of imidazole (9.99 g, 146.8 mmol) and 1,2-butylene oxide (10.59 g, 146.8 mmol) was placed in a round-bottomed flask and stirred at 60 °C for 72 h. Purification of the resulting crude product by column chromatography [$CHCl_3$/MeOH (8:2)] afforded a yellowish oil (20.42 g, 145.67 mmol, yield 99%).

1-(1*H*-1,2,4-Triazol-1-yl)butan-2-ol [(±)-3b]: A mixture of 1,2,4-triazole (7 g, 101.4 mmol) and 1,2-butylene oxide (8.77 g, 121.63 mmol) was placed in a round-bottomed flask and stirred at 70 °C for 24 h. The resulting crude product was purified by column chromatography [$CHCl_3$/MeOH (95:5)] to afford a yellowish oil (13.78 g, 97.61 mmol, yield 96%).

1-(1*H*-Imidazol-1-yl)butan-2-yl Acetate [(±)-4a]: A mixture of pyridine (4.5 mL, 4.38 g, 55.74 mmol), acetic anhydride (0.39 mL, 0.41 g, 4.04 mmol), and DMAP (30 mg) was cooled to 0 °C, and 1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (0.54 g; 3.85 mmol) was added. The mixture was stirred at room temperature for 72 h. The pyridine was then evaporated under reduced pressure, and the reaction was quenched with saturated $NaHCO_3$ solution (7.5 mL) and extracted with AcOEt (3 × 5 mL). The organic phases were combined and condensed by using a rotary evaporator. The residue was dissolved in toluene (20 mL), and the solvents were evaporated to dryness. The product was purified by column chromatography [$CHCl_3$/MeOH (95:5)] to afford a yellowish oil (0.45 g, 2.47 mmol, yield 64%).

1-(1*H*-1,2,4-Triazol-1-yl)butan-2-yl Acetate [(±)-4b]: To a solution of 1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (0.3 g, 2.13 mmol) in 2-methyl-2-butanol (2.5 mL), vinyl acetate (0.91 g, 10.62 mmol, 0.98 mL) and Novozym SP 435 (0.1 g) were added. The reaction mixture was stirred at room temperature with a magnetic stirrer for 48 h. Aliquots were regularly analyzed by GC until almost 100% conversion was reached. The enzyme was removed by filtration, and the solution was evaporated to dryness. The crude product was purified by flash chromatography with gradient elution [$CHCl_3$/MeOH (9:1 to 8:2)] to afford a colorless oil (0.35 g, 1.93 mmol, yield 91%).

1-Acetoxy-2-methylcyclohexene[19] (9): A solution of 2-methylcyclohexanone (30 g, 267.5 mmol, 32.5 mL) in CCl_4 (146 mL) was cooled to 0 °C. Acetic anhydride (54.6 g, 534.9 mmol, 50.56 mL) and a catalytic amount of aqueous $HClO_4$ solution (60%) were added, and the mixture was stirred at room temperature for 24 h. The flask content was diluted with Et_2O (250 mL), washed with saturated $NaHCO_3$ aqueous solution (3 × 200 mL), and the organic phases were combined and dried with anhydrous Na_2SO_4. After filtration and solvent evaporation under reduced pressure, the residue was purified by vacuum distillation to give a colorless oil (30.4 g, 197.2 mmol, yield 74%, bp 28–28.5 °C, p = 0.05 Torr).

Kinetic Resolution

Lipase-Catalyzed Kinetic Resolution of Racemic (±)-1-(1*H*-Imidazol-1-yl)butan-2-ol [(±)-3a]: Racemic 1-(1*H*-imidazol-1-yl)butan-2-ol (1 g, 7.13 mmol) was dissolved in 2-methyl-2-butanol (10 mL).

Amano PS-IM lipase (0.3 g, 150 U) and 1-acetoxy-2-methylcyclohexen (2.2 g, 14.26 mmol) were added. The reaction mixture was agitated (250 rpm) at room temperature. Aliquots were regularly analyzed by GC until ca. 52% conversion was reached. The enzyme was removed by filtration and rinsed with 2-methyl-2-butanol (15 mL), and the solutions were concentrated under reduced pressure. The products were separated by flash chromatography [$CHCl_3$/MeOH (9:1)] to afford (*S*)-(+)-1-(1*H*-imidazol-1-yl)butan-2-ol (+)-**5a** [440 mg, 88% isolated yield; *ee* = 98%. $[\alpha]_D^{29}$ = +25.1 (*c* = 1.0, $CHCl_3$)] and (*R*)-(+)-1-(1*H*-imidazol-1-yl)butan-2-yl acetate (+)-**6a** [590 mg, 91% isolated yield; *ee* = 80%. $[\alpha]_D^{29}$ = +12.3 (*c* = 1.0, $CHCl_3$)]. For additional data, see Table 2.

Lipase-Catalyzed Kinetic Resolution of Racemic (±)-1-(1*H*-1,2,4-Triazol-1-yl)butan-2-ol [(±)-3b]: Racemic 1-(1*H*-1,2,4-triazol-1-yl) butan-2-ol (1 g, 7 mmol) was dissolved in 2-methyl-2-butanol (5 mL). Amano PS-IM lipase (0.3 g, 150 U) and 1-acetoxy-2-methylcyclohexene (2.73 g, 17.7 mmol) were added. The reaction mixture was agitated at room temperature at 250 rpm. Aliquots were regularly analyzed by GC until approximately 51% conversion was reached. The reaction was stopped by removing the catalyst by filtration. The enzyme was washed with 2-methyl-2-butanol (8 mL) and methanol (5 mL), and the combined solutions were evaporated to dryness. The products were separated by flash chromatography [$CHCl_3$/MeOH (95:5)] to afford (*S*)-(+)-1-(1*H*-1,2,4-triazol-1-yl)-butan-2-ol (+)-**5b** [305 mg, 61% isolated yield; *ee* > 99%. $[\alpha]_D^{29}$ = +48 (*c* = 1.0, $CHCl_3$)] and (*R*)-(+)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-yl acetate (+)-**6b** [370 mg, 57% isolated yield; *ee* = 95%. $[\alpha]_D^{29}$ = +23 (*c* = 1.0, $CHCl_3$)]. For additional data, see Table 3.

General Procedure for Determination of the Absolute Configuration of (+)-5a and (+)-5b

Esterification of (*S*)-(+)-1-(1*H*-imidazol-1-yl)butan-2-ol [(+)-5a] with (*R*)- or (*S*)-α-Methoxy-α-phenylacetic Acid: To a solution of (*S*)-(+)-1-(1*H*-imidazol-1-yl)butan-2-ol (50 mg, 0.36 mmol), a catalytic amount of DMAP (5 mg), (*R*)- or (*S*)-α-methoxy-α-phenylacetic acid (59 mg, 0.36 mmol), and *N*,*N*′-dicyclohexylcarbodiimide (DCC, 88 mg, 0.43 mmol) in dry CH_2Cl_2 (2.5 mL) were added. After 24 h of stirring at room temp., precipitated dicyclohexylurea was removed by filtration and the urea cake was rinsed with toluene (3× 5 mL). The combined solutions were evaporated, and the product was purified on a preparative chromatographic plate with a mixture of hexane/ethyl acetate (1:1) as the eluent.

Esterification of (*S*)-(+)-1-(1*H*-1,2,4-Triazol-1-yl)butan-2-ol [(+)-5b] with (*R*)- or (*S*)-α-Methoxy-α-phenylacetic Acid: A catalytic amount of DMAP (5 mg) and DCC (87.7 mg, 0.42 mmol) were added to a solution of (*S*)-(+)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (50 mg, 0.35 mmol) and (*R*)- or (*S*)-α-methoxy-α-phenylacetic acid (59 mg, 0.35 mmol) in dry CH_2Cl_2 (2.5 mL). After 24 h of stirring at room temp., precipitated dicyclohexylurea was removed by filtration, and the urea cake was rinsed with toluene (3× 1.5 mL). The combined solutions were washed with cold HCl (1 M, 2× 1 mL), saturated $NaHCO_3$ (2× 1 mL), and saturated NaCl (1 mL). After drying the solution over anhydrous $MgSO_4$ and evaporation of the solvent, the product was purified on a preparative chromatographic plate with a mixture of hexane/ethyl acetate (1:1) as the eluent.

General Methods for the Preparation of Chiral Ionic Liquids

Synthesis of Optically Active Imidazolium Salts (+)-7a–i: (*S*)-(+)-1-(1*H*-Imidazol-1-yl)butan-2-ol (0.5 g, 3.57 mmol) was dissolved in dry CH_3CN (5 mL) and subsequently a threefold molar excess of the appropriate freshly distilled alkyl bromide or iodide was added. The reaction mixture was stirred under the conditions given in Table 5. The reaction progress was monitored by TLC with a chloroform/methanol (8:2) mixture as the eluent. The reaction mixture was cooled to room temperature, and the separated salt was washed with Et_2O (3× 5 mL) to afford a dark oil, which was sequentially purified from tars with a column filled with active carbon. The resulting product was a colored oil.

Synthesis of Optically Active Triazolium Salts (+)-8a–f: Optically active (*S*)-(+)-1-(1*H*-1,2,4-triazol-1-yl)butan-2-ol (0.5 g, 3.54 mmol) was dissolved in dry CH_3CN (5 mL), and a threefold molar excess of the appropriate freshly distilled alkyl bromide or iodide was added. The reaction mixture was stirred under the conditions given in Table 5. The reaction progress was monitored by TLC with a chloroform/methanol (8:2) as eluent. The reaction mixture was cooled to room temperature, and the resulting precipitate was removed by filtration and washed with Et_2O (5× 5 mL). The solvent was removed under reduced pressure to yield the product as a solid or colored sticky oil.

Microorganisms Used: The strains of the American Type Culture Collection (ATCC): *Escherichia coli* ATCC 8739, *Salmonella typhimurium* ATCC 14028, *Pseudomonas aeruginosa* ATCC 9027, *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538, *Candida albicans* ATCC 10231, *Aspergillus brasiliensis* ATCC 16404. The strains received from the IHAR-PIB collection of Plant Breeding and Acclimatization Institute, Młochów: *Colletotrichum coccodis* MC 1, *Fusarium culmorum* MF 18, *Fusarium oxysporum* MF 5, *Fusarium sambucinum* MF 1, *Phytophthora infestans* MP 324, *Phytophthora infestans* MP 1320.

Antimicrobal Activity Assays: A qualitative evaluation of antimicrobal activity was determined by the agar diffusion method of Rebros et al.[26] with some modifications. Bacterial lawns were grown in liquid tryptic soy broth (TSB, Merck) medium for 24 h. Inocula of approximately 2.5–3.5 × 10^8 CFU/mL (200 μL, CFU = colony forming unit) were spread on solid tryptic soy agar (TSA, Merck) medium. Subsequently, sterile 8 mm paper discs were placed on the surface of the agar, and the IL (20 μL, 0.025 M) was added. The plates were incubated for 24 h at 30 °C and the diameter of the growth inhibition zones were measured to the nearest millimeter. Each test was performed in duplicate. The ILs used in the experiment were diluted with 0.1–1% of EtOH. It was verified in a separate experiment that EtOH at a concentration of 0.1–1% did not inhibit bacterial growth by itself (data not shown).

A quantitative evaluation of antimicrobal activity was determined by the tube dilution method.[27] Bacterial and yeast strains were cultured for 24 h on TSB (Merck) medium. The ILs were diluted in TSB medium and subsequently the same amount of inoculum was added to each tube. A positive control was prepared without ILs. The growth (or lack thereof) of the microorganisms was determined visually after incubation for 24 h at 30 °C. The lowest concentration at which there was no visible growth (turbidity) was taken as the minimal inhibitory concentration (MIC).

The antifungal activity was evaluated by measuring the inhibition of radial growth on an agar medium in a petri dish (Liu et al.).[28] The ILs were dissolved in EtOH (96%). Subsequently, the appropriate diluted ILs were added to a potato dextrose agar (PDA, Merck) medium or in the case of *P. infestans* strains to a rye agar[29] medium to give a final concentration of 1 mM of IL and less than 0.1% of ethanol. The 8 mm disks were cut from an actively growing mycelium of the fungi and placed in the center of the agar plate containing the proper dilution of IL. The positive control was prepared without IL. The radial growth of the fungal colonies was measured after several days of incubation at 25 °C (18 °C for the *P. infestans* strains). The inhibitory activity of the ILs was expressed as a percentage of the positive control growth. Each experiment

was repeated twice and the data presented here are the average of two experiments.

Supporting Information (see footnote on the first page of this article): Characterization data for all compounds.

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