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PAPER

From plant to drug: ionic liquids for the reactive dissolution of biomass†‡

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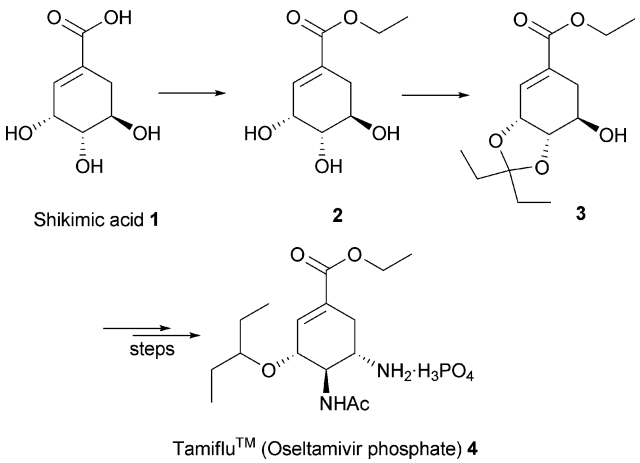
We present an ionic liquid (IL) strategy for the reactive dissolution of star anise seeds using different Brønsted-acidic ionic liquids as the solvent and reaction media towards the isolation of important pharmaceutical intermediates; this procedure provides a single-step, higher yielding and environmentally benign strategy towards the synthesis of the anti-influenza drug Tamiflu™.

Introduction

To date, extraction of active ingredients from plant material is mainly performed using solvent extraction processes; however this is often associated with the dangers of handling large volumes of volatile and combustible solvents, human risk and safety issues, and also with poor extraction efficiency that can be the bottleneck in a drug's production.[1] This is particularly true for shikimic acid ((3*R*,4*S*,5*R*)-3,4,5-trihydroxycyclohex-1-ene-1-carboxylic acid, **1**), the major starting material for the production of the neuraminidase inhibitor Tamiflu™ (Oseltamivir phosphate, **4**) which is well known for the treatment and prevention of influenza.[2,3] Although alternative fermentation processes for shikimic acid have been developed, the production of oseltamivir phosphate is still dependent on the isolation of shikimic acid **1** from Chinese star anise seeds (*Illicium verum*), and the low isolation yield of 3–7% was held responsible for the world-wide shortage in Tamiflu™ in 2005.[4–6] In the current manufacturing process, the synthesis of Oseltamivir phosphate **4** involves the formation of shikimic acid ethyl ester **2** followed by an acetonide or diethyl ketal intermediate **3** that is subsequently transferred into the final drug (Scheme 1).[7]

The initial esterification step is typically done using stoichiometric amounts of toxic and corrosive thionyl chloride for the generation of anhydrous hydrochloric acid as catalyst. The toxicity of thionyl chloride as well as the formation of greenhouse gases after hydrolisation do not only raise serious safety and environmental concerns, but also require a more involved manufacturing process. Recently, Roche reported a streamlined process for the direct formation of ketal intermediate **3** without thionyl chloride by using the preformed reagent 3,3-diethoxypentane.[8,9] However, it should be noted that this optimised procedure requires the use of pure shikimic acid in rather high and consistent quality. Hence, novel approaches are required to feed the growing demand for Tamiflu™ *via* an environmentally friendly process, and also to improve technologies for the better isolation of pharmaceutically active ingredients from plant matter .



Scheme 1 Synthesis of Tamiflu™ from shikimic acid **1**.

Since the pioneering work by Rogers *et al.* in 2002 there has been tremendous interest in the application of ionic liquids (ILs, defined as salts melting below 100 °C) as solvents for cellulosic biomass.[10,11] While research primarily focuses on processing, derivatisation or degradation of biomass, only limited attention has been paid to the isolation of active components from biomass. Although promising work towards the isolation of the antimalaria drug artemisinin was reported in 2005, it was only recently that MacFarlane *et al.* presented an elegant and efficient strategy for the isolation of tannins from plant materials using a distillable protic ionic liquid (DIMCARB, *N*,*N*-dimethylammonium *N*,*N*-dimethylcarbamate) as novel

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† Electronic supplementary information (ESI) available: Calibration curves, copies of chromatograms and spectra of pure and crude active components **2**–**4**. See DOI: 10.1039/c1gc15058h

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extraction media.[12,13] Similarly, a set of imidazolium based ionic liquids has been used for the extraction of piperine from white pepper and of the flavonoid rutin (3,3′,4′,5,7-pentahydroxyflavone-3-β-D-rutinoside) from traditional Chinese medical plants applying either ultrasound- or microwave-assisted extraction methods.[14,15]

A special role in the large pool of ionic liquids that are available for biomass processing can be attributed to functionalised ionic liquids, *e.g.* sulfonic acid modified ionic liquids that play a double role as solvent, but also as catalyst.[16] These Brønsted-acidic ionic liquids have been reported as catalysts for a variety of acid-catalysed organic reactions, *e.g.* esterification, but also for the hydrolysis and decomposition of cellulose or lignocellulosic biomass into fermentable sugars.[17,18]

The dual role of these functionalised ionic liquids motivated us to expand the scope of active ingredient isolation using ionic liquids for the direct formation of drug intermediates from crude biomass. Herein, we report the reactive dissolution of star anise in the presence of Brønsted-acidic ILs as solvent and catalyst for the formation of shikimic acid ethyl ester **2** and for the *in situ* formation of ketal ester **3** to develop an improved process for Oseltamivir phosphate (Tamiflu™) production.

Results and discussion

HPLC analysis

In order to efficiently screen different ionic liquids as solvents and catalysts for the reactive dissolution of biomass, we developed an HPLC strategy. Since the determination of a highly polar analyte such as shikimic acid can be difficult in the presence of ionic liquids, HPLC analysis was preferably done with an ion exchange column and H_2O/5% trifluoroacetic acid as eluent to allow the direct and simultaneous determination of shikimic acid **1** and shikimic acid ethyl ester **2** in the presence of various ionic liquids. Calibration curves were obtained using phenol as an internal standard and were linear in a range from 2 mg ml^{-1}–0.01 mg ml^{-1} with excellent correlation coefficients $R^2 > 0.999$ (see ESI, Fig. S1 and Fig. S2†). In a typical chromatogram shikimic acid **1** and shikimic acid ethyl ester **2** were eluated after a retention time of t_r = 6.0 min and t_r = 9.3 min, respectively, and did not interfere with any by-products from lignocellulose degradation, thus allowing the direct determination of isolation yield and conversion from the crude biomass extract (Fig. 1).

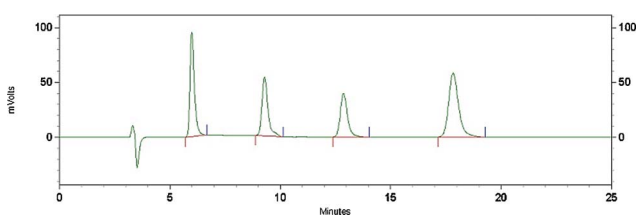

Fig. 1 Representing chromatogram displaying shikimic acid **1** (t_r = 6.0 min), shikimic acid ethyl ester **2** (t_r = 9.3 min), ionic liquid [HSO_3C_4mim]NTf_2 **8** (t_r = 12.9 min) and phenol as internal standard (t_r = 17.8 min).

Esterification of shikimic acid

Initially, we investigated the esterification of pure shikimic acid in the presence of different Brønsted-acidic ionic liquids.

In addition to the commercially available acidic ionic liquid [C_2mim]HSO_4 **10** and the protic ionic liquid [HC_2im]HSO_4 **11**, a small selection of sulfonic acid functionalised ionic liquids **5–9** that could be easily obtained by the addition of a stoichiometric amount of a protic acid to the zwitterionic intermediate obtained from *N*-methylimidazole and 1,4-butanesultone (Fig. 2) were also tested.

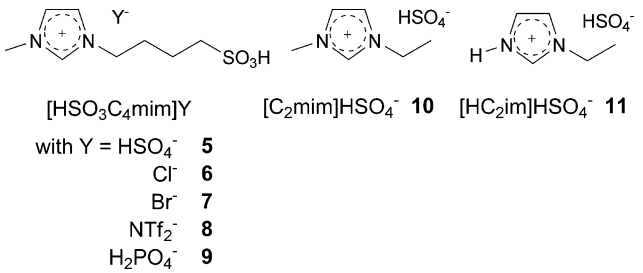

Fig. 2 Acidic ionic liquids used in this study.

Esterification of shikimic acid was typically performed using stoichiometric amounts of ionic liquid in an excess of anhydrous EtOH for 24 h at 80 °C (Table 1).

We found that sulfonic acid functionalised ionic liquids are suitable catalysts for the esterification of shikimic acid: the double acidic hydrogensulfate ionic liquid as well as the halide salts showed good to excellent conversion to the ethyl ester (Table 1, entry 1–5). The catalytic performance might be explained by the acidity of these functionalised ILs: Xu *et al.* performed UV-vis studies and reported the acidity of [HSO_3C_4mim]Y to increase in the order Y = HSO_4^- > Br^- > Cl^-.[19] Best results were obtained using the bistriflimide ionic liquid [HSO_3C_4mim]NTf_2 **8**, and complete conversion of the acid was observed. The reaction time could be considerably shortened using microwave irradiation, and 88% yield was obtained after 30 min irradiation time only at 100 °C. As the only exception in the set of sulfonic acid functionalised ILs, [HSO_3C_4mim]H_2PO_4 **9** failed as catalyst for the esterification, since a neglible yield of 6% only was observed (entry 7). The low

Table 1 Esterification of shikimic acid **1** catalysed by different Brønsted-acidic ionic liquids

Entry	Ionic liquid	Conditions[a]	Yield [%][b]
1	[HSO_3C_4mim]HSO_4 **5**	1 eq	96
2	[HSO_3C_4mim]HSO_4 **5**	0.1 eq	95
3	[HSO_3C_4mim]HSO_4 **5**	1 eq[c]	88
4	[HSO_3C_4mim]Br **6**	1 eq	84
5	[HSO_3C_4mim]Cl **7**	1 eq	81
6	[HSO_3C_4mim]NTf_2 **8**	1 eq	99
7	[HSO_3C_4mim]H_2PO_4 **9**	1 eq	6
8	[C_2mim]HSO_4 **10**	1 eq	3
9	[HC_2im]HSO_4 **11**	1 eq	14
10	H_2SO_4	1 eq	83

[a] Performed with 1 mmol of shikimic acid and 1 ml of anhydrous EtOH for 24 h at 80 °C. [b] Determined *via* HPLC analysis using phenol as the internal standard. [c] Performed under microwave irradiation for 30 min at 100 °C.

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activity here might be explained by an incomplete protonation of the imidazolium side chain sulfonic acid, and it seems that the equilibrium here is rather shifted towards the zwitterionic precursor and phosphoric acid.

Similarly, only low conversion was obtained with $[C_2mim]HSO_4$ **10** or the protic ionic liquid $[HC_2im]HSO_4$ **11**, thus indicating that the sulfonic acid group in the side chain of the cation is responsible for the catalytic activity in this reaction (entry 10 and 11). In comparison, a lower conversion and 83% yield only were observed when using stoichiometric amounts of concentrated sulfuric acid as catalyst.

Reactive dissolution of star anise seeds

Once the catalytic activity of several ionic liquids had been established for pure shikimic acid, reactive dissolution of star anise powder was carried out. We decided to work with 100.0 ± 5.0 mg of star anise powder in a 10 wt% solution in ionic liquid/anhydrous EtOH mixtures and initially screened different ratios of ionic liquid and EtOH (Fig. 3).

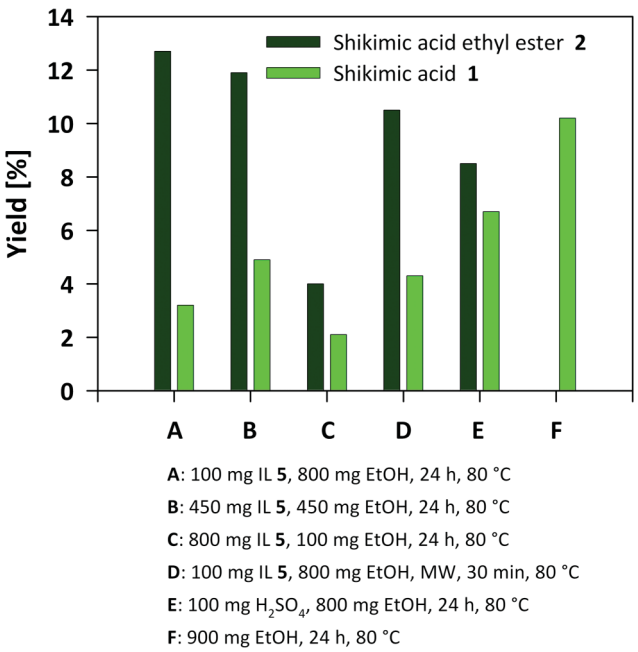

Fig. 3 Reactive dissolution of star anise: dependence on different reaction conditions.

We found that the highest conversion of shikimic acid was observed when a mass-equivalent amount of ionic liquid $[HSO_3C_4mim]HSO_4$ **5** was used, and 12.7% yield of shikimic acid ethyl ester **2** were obtained.§

When the ionic liquid was increased to 450 mg – corresponding to a 10 wt% solution of star anise in ionic liquid/EtOH 1 : 1 – the total extraction yield of shikimic acid **1** and ester **2** increased, indicating that an excess of ionic liquid leads to a better processing of biomass with comparable conversion towards the ester. However, when we further increased the amount of ionic liquid to 800 mg, isolation yield and conversion are significantly lower, which can probably be explained by the comparably high viscosity of the almost unstirrable sample. Furthermore, EtOH might not only act as reagent for the esterification, but also as co-solvent for the extraction process, and thus a reduction of EtOH results in the lower yield. Again, we could significantly lower the reaction time using microwave irradiation, although slightly lower isolation yields and conversions were obtained when the samples were irradiated for 30 min at 100 °C. In comparison, sulfuric acid alone also gave moderate results, although conversion and isolation yield are considerably lower than the results obtained with several acid functionalised ionic liquids.

When comparing different ionic liquids we found a similar pattern as we have observed with pure shikimic acid (Fig. 4, *cf.* Table 1). With the exception of hydrogenphosphate ionic liquid **9**, all sulfonic acid functionalised ionic liquids **5–8** performed equally well and gave good conversion and extraction yield. Again, $[C_2mim]HSO_4$ **10** or the protic ionic liquid $[HC_2im]HSO_4$ **11** did not catalyse the esterification of shikimic acid, and only very small amounts of **2** were produced.

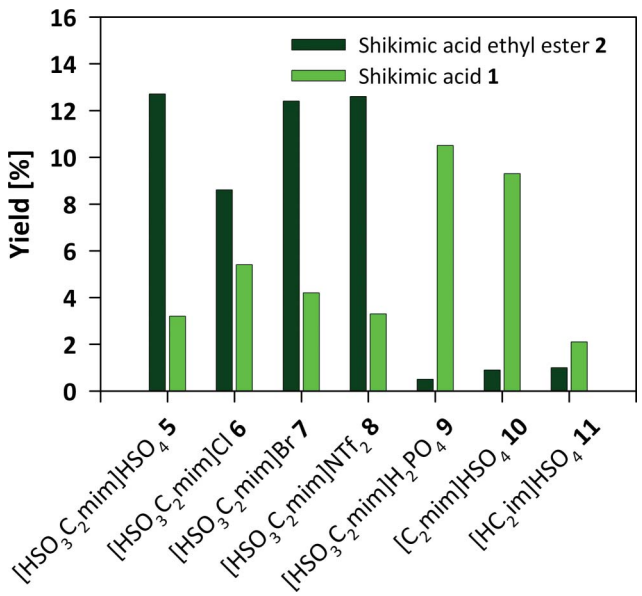

Fig. 4 Reactive dissolution of star anise: dependence on ionic liquids using 100.0 ± 5.0 mg star anise, 100.0 ± 5.0 mg IL and 800 mg EtOH.

In situ formation of ketal intermediate 3 from star anise

In the course of Roches's total synthesis of Oseltamivir phosphate, the formation of shikimic acid ethyl ester is followed by another acid-catalysed process.[7] This motivated us to develop an *in situ* formation of ketal intermediate **3** from star anise powder using Brønsted-acidic ionic liquids as solvent and catalyst.

For initial experiments, we investigated the reaction of pure shikimic acid **1** in a 1 : 1 mixture of ethanol and 3-pentanone catalysed by one equivalent of the Brønsted-acidic ionic liquids **5** or **8** (Scheme 2). When performing HPLC analysis of the crude

§ The extraction yield of shikimic acid ethyl ester **2** was defined as: yield [%] = (mass of shikimic acid ethyl ester **2** from HPLC × 100)/mass of star anise powder. The extraction yield of shikimic acid **1** and ketal intermediate **3** is reported accordingly.

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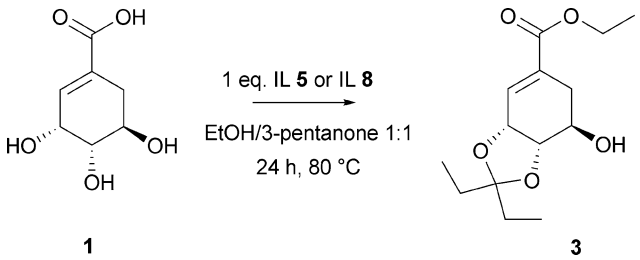

Scheme 2 Ionic liquid-catalysed formation of ketal intermediate **3**.

reaction mixture, we were pleased to observe the *in situ* formation of ketal intermediate **3** in 68% and 79% yield after 24 h at 80 °C, respectively. This reaction could be also catalysed by sulfuric acid – when using one equivalent of H_2SO_4 as the catalyst under similar conditions, we observed a good conversion and 70% yield of ketal intermediate **3**.

Based on our previous experience, we repeated this reaction with star anise powder in a 10 wt% solution of Brønsted-acidic ionic liquid, EtOH and 3-pentanone for 24 h at 80 °C.

We decided to scale-up the reaction at this step to 1 g of star anise powder and isolate the crude extract. After the given reaction time, the reaction mixture was hydrolysed with aqueous $NaHCO_3$ solution, the remaining biomass was removed *via* filtration and the crude mixture extracted with ethyl acetate. This extraction process allowed not only to separate any unreacted shikimic acid, but could also remove water soluble degradation products such as sugars that are formed during the acid-catalysed hydrolysis of lignocellulosic biomass. The crude extract was further treated with charcoal and, after distillation of ethyl acetate, ketal **3** was obtained as a light yellow oil.

Considering the origin directly from biomass, surprisingly high purities of ~80% were obtained for the isolated extract, as was assessed with GC-MS, HPLC and NMR analysis (Fig. 5, ESI Figs. S3 and S4†).

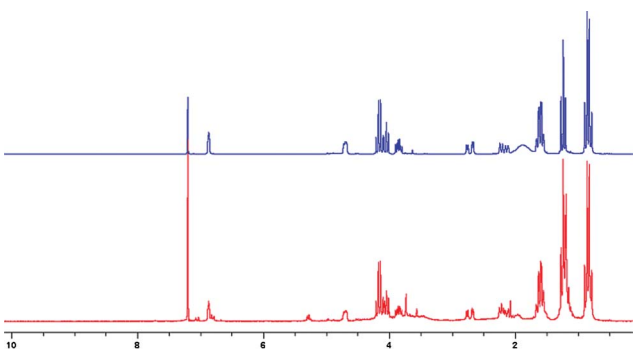

Fig. 5 ^{1}H NMR spectra of pure (top) and crude (bottom) ketal intermediate **3** obtained after extractive work-up.

The yield of ketal intermediate **3** was determined *via* HPLC using a conventional reversed phase column and CH_3CN–H_2O as eluent with phenol as the internal standard (ESI Fig. S5†). Again, we found excellent catalytic activity with the sulfonic acid functionalised ionic liquids $[HSO_3C_4mim]HSO_4$ **5** and $[HSO_3C_4mim]NTf_2$ **8**, thus allowing to obtain ketal **3** directly from star anise powder in a single step (Table 2, entries 1–8). In

Table 2 *In situ* formation of ketal intermediate **3** from star anise with different Brønsted-acidic ionic liquids

Entry	Ionic liquid	IL [g]/EtOH [g]/ 3-pentanone [g][a]	Yield[b]
1	$[HSO_3C_4mim]HSO_4$ **5**	0.1/4.45/4.45	1.0
2	$[HSO_3C_4mim]HSO_4$ **5**	0.5/4.25/4.25	4.5
3	$[HSO_3C_4mim]HSO_4$ **5**	1/4/4	6.9 (6.1)[d]
4	$[HSO_3C_4mim]HSO_4$ **5**	4.5/2.25/2.25	10.4 (10.3)[d]
5	$[HSO_3C_4mim]HSO_4$ **5**	1/4/4[c]	6.1 (5.9)[d]
6	$[HSO_3C_4mim]NTf_2$ **8**	1/4/4	9.6 (8.8)[d]
7	$[C_2mim]HSO_4$ **10**	1/4/4	<0.1
8	$[HC_2im]HSO_4$ **11**	1/4/4	0.5
9	H_2SO_4	1/4/4[e]	6.2
10	—	0/4.5/4.5	<0.1

[a] Performed using 1.00 ± 0.05 g star anise powder for 24 h at 80 °C. [b] Determined *via* HPLC analysis from the crude product. [c] Performed under microwave irradiation for 30 min at 100 °C. [d] Isolated yield after preparative HPLC in paranthesis. [e] Performed using 1.0 g of H_2SO_4 for 24 h at 80 °C.

contrast to the esterification of star anise, an increase of ionic liquid led to a better yield of ketal **3**, and a maximum yield of 9.6% of ketal **3** could be obtained using 1 g of ionic liquid $[HSO_3C_4mim]NTf_2$ **8** as solvent and catalyst.

For verification, we isolated the ketal intermediate **3** *via* preparative HPLC and obtained the pure compound in 10.3% yield. However, it should be noted that this purification process is not necessary for the subsequent conversion to Tamiflu™: The crude ketal **3** can be directly mesylated, as described for the synthesis of Oseltamivir phosphate **4**, and complete conversion towards the next intermediate of the total synthesis was observed in 30 min under standard literature procedures.[7] Although this extraction process does not allow the recovery of the ionic liquid, this process does not only eliminate the use of toxic and corrosive thionyl chloride, but simplifies the industrial three-step process into a simple one-step procedure with improved yield. Furthermore, this allows a more efficient use of the limiting natural resource compared to the current manufacturing of Tamiflu™ that is limited by the low isolation yield of shikimic acid of 3–7% in the first step.

Conclusions

We have shown that acidic functionalised ionic liquids can be successfully used for the reactive dissolution of star anise. For the first time, the pharmaceutically active ingredient was not only isolated from biomass using ionic liquids, but efficiently transferred into shikimic acid ethyl ester **2**, or ketal intermediate **3** that are both important precursors of Oseltamivir phosphate (Tamiflu™). Given the growing world-wide demand for anti-influenza drugs, this novel strategy provides a single-step, higher yielding and environmentally benign strategy for the manufacturing of the anti-influenza drug Tamiflu™. Reactive dissolution of biomass using functionalised ionic liquids should therefore be considered as another tool in drug development, and might lead to new and improved technologies for the isolation and processing of pharmaceutically active ingredients from plant matter.

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Materials and methods

All chemicals unless otherwise stated were purchased from commercial suppliers and used without further purification. Star anise powder was purchased on a local market and used as received. *N*-Methylimidazole was distilled from KOH prior to use. 1-Methyl-3-(4-sulfobutyl)-imidazolium zwitterion was prepared following literature methods.[16] Functionalised ionic liquids **5**,[20] **6**,[17] **7**,[17] **8**[21] and **9**[17] and the protic ionic liquid **11** were prepared as previously reported, and analytical data were in accordance with literature. All ionic liquids were dried for 24–48 h at 80 °C and 0.01 mbar with stirring before use and were stored under Argon. Analytical standards of shikimic acid ethyl ester **2** and ketal intermediate **3** were prepared according to literature procedures and purified *via* repeated crystallisation or preparative HPLC.[7]

Microwave reactions were performed on a BIOTAGE Initiator™ sixty microwave unit. The reported times are hold times.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 at 200 and 50 MHz, respectively, using the solvent peak as reference. *J* values are given in Hz. ^{13}C NMR spectra were run in proton-decoupled mode and multiplicities from DEPT were referred as s (singlet), d (doublet), t (triplet) and q (quartet).

HPLC analysis was performed on a Thermo Finnigan Surveyor chromatograph equipped with a PDA plus (190–360 nm) and refractive index (RI) detector. For analysis of shikimic acid **1** and shikimic ester **2**, a Phenomenex Resex RHM-monosaccharide H^+ column (150 × 7.80 mm) was used as the stationary phase with H_2O/5% trifluoroacetic acid as solvent and a flow rate of 0.6 ml min^{-1}; detection was done *via* refractive index (*Method A*). For the determination of ketal **3**, a Phenomenex Luna 10 µm C18(2) 100A column (250 × 4.60 mm) was used with CH_3CN–H_2O 50/50 as the solvent and a flow rate of 1 ml min^{-1}; detection was done at 210 nm (*Method B*).

Preparative HPLC was performed on a Shimadzu LC-8A device with a SIL-10AP autosampler, SPD-20A dectector and FRC-10A fraction collector. For separation, a Phenomenex Luna 10 µm RP18(2) 100A (250 × 21.20 mm) was used with CH_3CN–H_2O 40/60 as solvent and a flow rate of 20 ml min^{-1}. The injection volume was 3 ml and the detection wavelength was 210 nm.

GC–MS analyses were conducted on a VOYAGER Quadrupol (Thermo Finnigan) directly interfaced to a GC 8000 TOP gas chromatograph using a BGB-5 (30 m × 0.32 mm i.d., 1.0 µm film thickness) cross-bonded dimethyl polysiloxane capillary column. The oven program temperature was 80 °C (2 min)//10 °C min^{-1}//280 °C (3 min). Source and transfer line temperatures were set at 200 and 280 °C, respectively.

General procedure for the formation of (3*R*,4*S*,5*R*)-3,4,5-trihydroxycyclohex-1-ene-1-carboxylic acid, ethyl ester 3 (shikimic acid ethyl ester)

A 5 ml screw-cap vial was charged with shikimic acid **1** (17.4 mg, 1 mmol), 3-methyl-1-(4-sulfobutyl)imidazolium bistriflimide $[HSO_3C_4mim]NTf_2$ **8** (49.9 mg, 1 mmol) and 1 ml of anhydrous EtOH and heated with stirring for 24 h at 80 °C.

HPLC analysis: The sample was diluted with water to 10.0 ml. A sample of 1.0 ml was taken and 0.2 ml of a phenol stock solution (250.0 mg in 100 ml H_2O) were added. The samples were directly analyzed *via* HPLC according to *Method A*.

General procedure for the microwave assisted reactive dissolution of star anise powder

A microwave vial (5 ml) was charged with 100.0 mg of star anise powder, 100 mg of 3-methyl-1-(4-sulfobutyl)imidazolium hydrogensulfate $[HSO_3C_4mim]HSO_4$ **5** and 800 mg of anhydrous EtOH, sealed with a Teflon septum and heated for 30 min at 80 °C under microwave irradiation (high absorption level). Water (50 ml) was added to the resulting black residue and thoroughly mixed.

HPLC analysis: A sample of 1.0 ml was immediately taken from the clear supernatent solution and 0.2 ml of a phenol stock solution (250.0 mg in 100 ml H_2O) were added. The samples were centrifuged for 10 min at 13000 min^{-1}, and the supernatent was directly analysed *via* HPLC according to *Method A*.

General procedure for the *in situ* formation of (3a*R*,7*R*,7a*S*)-2,2-diethyl-3a,6,7,7a-tetrahydro-7-hydroxy-1,3-benzodioxole-5-carboxylic acid, ethyl ester 3

A 5 ml screw-cap vial was charged with shikimic acid **1** (17.4 mg, 1 mmol), 3-methyl-1-(4-sulfobutyl)imidazolium bistriflimide $[HSO_3C_4mim]NTf_2$ **8** (49.9 mg, 1 mmol), 0.5 ml of anhydrous EtOH and 0.5 ml of 3-pentanone and heated with stirring for 24 h at 80 °C.

HPLC analysis: A sample of 0.2 ml was immediately taken, diluted with 0.8 ml of CH_3CN and 0.2 ml of a phenol stock solution (50.0 mg in 100 ml CH_3CN) were added. The samples were directly analysed *via* HPLC according to *Method B*.

In situ formation of (3a*R*,7*R*,7a*S*)-2,2-diethyl-3a,6,7,7a-tetrahydro-7-hydroxy-1,3-benzodioxole-5-carboxylic acid, ethyl ester 3 from star anise powder

A large microwave vial (20 ml) with magnetic stirrer flee is charged with 1.0 g of star anise powder, 1.0 g of IL **5**, 4.0 g of EtOH and 4.0 g of 3-pentanone. The flask is sealed with a Teflon septum and heated at 80 °C (oil bath temperature) with stirring overnight. The mixture is poured into a saturated $NaHCO_3$ solution (50 ml), filtered and extracted 3 times with EtOAc. The combined organic layers are treated with charcoal, dried over Na_2SO_4, filtered over a batch of silica and evaporated to dryness. Remaining solvent traces are removed under reduced pressure (0.01 mbar) to give crude **3** as light yellow oil.

HPLC analysis: The sample was diluted with CH_3CN to 50.0 ml. A sample of 0.2 ml was taken, diluted with 0.8 ml of CH_3CN and 0.2 ml of a phenol stock solution (50.0 mg in 100 ml CH_3CN) were added. The samples were directly analysed *via* HPLC according to *Method B*.

Isolation: The crude product was further purified *via* preparative HPLC to give pure **3** as colourless oil in 10.3% yield.

δ_H (200 MHz; $CDCl_3$, Me_4Si) 0.87 (6 H, q, *J* 7.75), 1.27 (3 H, t, *J* 7.19), 1.64 (4 H, 2q, *J* 7.53), 2.22 (1 H, m), 2.55 (1 H, m), 2.74 (1 H, dd, J_1 17.37, J_2 4.70), 3.89 (1 H, m)), 4.10 (1 H, t, *J* 6.96), 4.19 (2 H, q, *J* 7.20), 4.74 (1 H, m), 6.90 (1 H, m). δ_C

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(50 MHz; $CDCl_3$, Me_4Si) 7.9 (q), 8.5 (q), 14.1 (q), 29.1 (t), 29.3 (t), 29.7 (t), 61.1 (t), 68.9 (d), 72.2 (d), 77.8 (d), 113.6 (s), 130.4 (s), 134.0 (s), 166.2 (s). GC-MS: t_r = 10.56 min, m/z 242 ($M^+ - C_2H_5$, 8%), 241 (61), 215 (7), 167 (19), 139 (78), 121 (19), 139 (78), 123 (9), 121 (22), 95 (95), 93 (11), 77 (11), 57 (100), 55 (9), 53 (10).

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