

VIP Very Important Paper

Selective Electrochemical Dibromination of Terpenes and Naturally Derived Olefins

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A simple electrochemical protocol is established for the selective alkene dibromination of naturally derived olefins, such as terpenes. The use of hazardous Br₂ or its analogues have been elegantly avoided by employing readily available, inexpensive, and harmless sodium bromide with a dual role as reagent and supporting electrolyte in combination with sustainable carbon-based electrodes. This electrochemical protocol

provides the desired products with good to excellent yields up to 82% with 10 examples. Scalability has been proved by a 5-fold scale-up. Notably, higher yields and selectivity were achieved in comparison to conventional bromination by Br₂ and DMSO/HBr system and the dibrominated compound was eligible for further functionalization, such as cyanation according to the Kolbe nitrile synthesis protocol.

Introduction

Converting renewable resources to biologically active molecules and functional materials are one of the hot topics among sustainable research fields.^[1–2] Terpenes are considered as one of the largest class of natural compounds with more than 50,000 different molecules identified, isolated and readily utilized by the pharmaceutical, agricultural and chemical industry.^[3–5] Multiple reports demonstrate antifungal,^[6–7] antiparasitic,^[8] antibacterial^[7,9] and anticancer^[10–12] properties of modified or even natural terpenes, like the naturally occurring brominated sesquiterpenoid, (–)-dactylone. The plant and fungi synthesized terpenes and terpenoids represent a valuable and inexpensive biomass resource and they are readily available in large scale from essential oils or as industrial by-products.^[13–14] For example, limonene, which is produced on 60,000 ton/year scale as the by-product of citrus juice industry.^[15–16] Their unique structural features enable versatile functionalization possibilities, hence it became a major spotlight in polymer chemistry in recent years.^[17–22] For these versatile application methods, terpenes represent one of the biggest renewable sources for conversion into valuable products. Nevertheless, the current

functionalization methods are accompanied with several difficulties. Chemical transformations such as isomerization, hydrolyzation, condensation and oxidation reactions are often accompanied with the formation of undesired by-products, reduced chemoselectivity and requires the utilization of several metal catalysts, such as Ru, Rh, Mn or Ni.^[23–24] Hence, to this date, selective transformation of such delicate molecules is still highly challenging.

The introduction of bromine groups for the functionalization of molecules is a well-known method, however it is not readily established for terpenes.^[25] Conventional methods for the dibromination of olefins usually employ hazardous and corrosive bromine,^[26–29] as well as the application of HBr or metal bromides in the presence of an external oxidant (Scheme 1).^[30–33] The utilization of next generation agents such as *N*-bromosuccinimide, pyridinium tribromide or hypervalent iodine reagents have also gained attention.^[34–36] While these agents enable simpler handling, their preparation is difficult and due to cost and atom economy aspects, a greener alternative is highly desired.

Oxidative electrochemistry provides a superior and “green” alternative to the traditional strategies. The use of electricity as a clean and inexpensive reagent diminishes waste generation and replaces the usually harmful redox reagents.^[37–41] Furthermore, constant current conditions in combination with carbon-based electrodes allow an easy and safe operation by simply switching on or off the electrochemical current.^[39,42–43] The electrochemical bromofunctionalization of alkenes including the generation of 1,2-vicinal dihalides have attracted special attention.^[44–50] Many great protocols have been reported recently for the electrochemical bromination of alkenes featuring direct electrochemical bromination,^[44–45] electrocatalytic bromination^[48] and bromination via linear paired electrosynthesis.^[46,49] Recently, the electrochemical bromofunctionalization of alkenes in a flow reactor was also reported.^[47] While these methods are widely applicable and provide good to excellent yields, they often utilize dangerous bromine sources, such as HBr,^[45,47] and depleting metal electrodes.^[44–48]

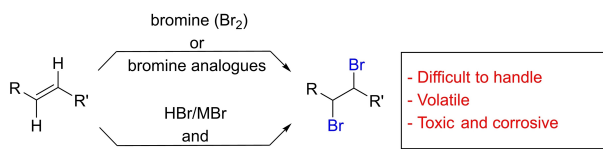
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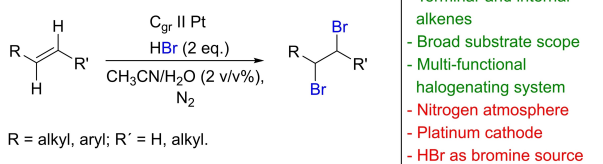
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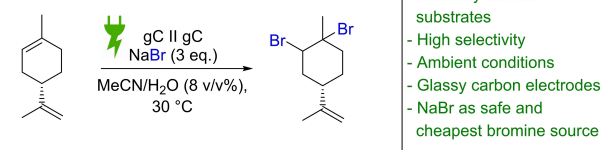
Conventional bromination of alkenes:



Direct electrochemical bromination: A. Lei et al.



This work:



Scheme 1. Synthetic strategies for the bromination of olefins, M = alkali metal, Cgr = graphite, gC = glassy carbon.

To overcome these drawbacks, a novel method for the trans-halogenation of numerous alkenes via an electron shuttle reaction was recently reported by our group.^[49] Nevertheless, while the electrochemical bromination of simple alkenes was extensively researched, the functionalization of naturally derived compounds and especially the dibromination of terpenes and terpenoids casts only very few examples.^[50]

This work presents a simple and sustainable electrochemical alternative to the already existing bromination methods extending the protocol to renewable resources in a selective manner. The implementation of naturally occurring terpenes and terpenoids facilitates a wide variety of brominated derivatives that can act as appropriate intermediates for further functionalization purposes. Employing inexpensive carbon-based electrodes such as graphite or glassy carbon instead of expensive platinum contributes to the principles of green chemistry.^[51–53] Sodium bromide acts both as the supporting electrolyte and a safe, bench-stable bromide source that can in-situ oxidised into bromine under ambient conditions. Moreover, to the best of our knowledge this method features the first electrochemical bromination of structurally challenging terpenes and terpenoids.

Results and Discussion

Initial optimization reactions were carried out in a PTFE undivided cell (see Supporting Information) according to Table 1. Readily available (4S)-(–)-limonene (**1**) was chosen as a test substrate as the presence of multiple functionalizable

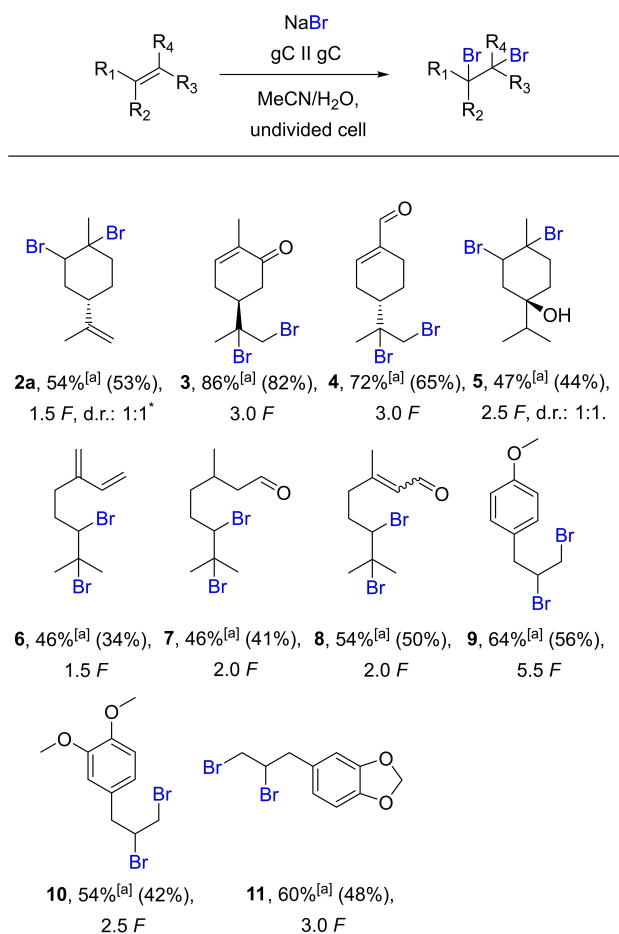
Table 1. Optimization of electrochemical dibromination of (4S)-(–)-limonene in 5 mL PTFE electrolysis cells, PTFE = polytetrafluoroethylene.

Entry	Deviation from standard conditions ^[a]	2a [%] ^[b]	2b [%] ^[b]
1	NBu ₄ Br	0	0
2	NEt ₄ Br	2	0
3	None	30	4
4	LiBr	32	6
5	divided cell	32	8
6	acetone/H ₂ O (8 v/v%)	52	4
7	HFIP/H ₂ O (8 v/v%)	0	0
8	MeCN/H ₂ O (20 v/v%)	9	0
9	gC gC	46	5
10	gC gC, 2.2 F	44	0
11	gC gC, 3.0 F	35	1
12	gC gC, <i>j</i> = 5 mA/cm ²	54	0

[a] Standard conditions: **1** (0.7 mmol), NaBr (2.1 mmol), MeCN/H₂O (5 mL, 8 v/v%), graphite electrodes, undivided cell, constant current, *j* = 20 mA/cm², 1.5 F (ref. terpene), 30 °C. [b] Yields determined by ¹H NMR (internal standard: CH₂Br₂). gC = glassy carbon.

double bonds offers regioselectivity issues. The first screening experiments revealed that **1** only tolerates NaBr (Table 1, Entry 1–4) which determines the composition of the solvent system obliging the presence of an additive. The utilization of LiBr as bromide salt provided equally great results, however, heavy cathode corrosion was observed. Under multiple solvent systems especially acetone/H₂O performed well with 52% of **2a**. However, due to the volatility of acetone solvent, further optimizations were carried on with MeCN/H₂O (see Supporting Information). The solvent/additive ratio also plays an important role in the outcome of the reaction. With increasing water content, the selectivity of the reaction decreases dramatically (Table 1, Entry 8). The reaction is highly selective towards the formation of **2a**, even after an increased amount of applied charge, there was no significant change in the yield of **2b** (see Supporting Information). When applying 1.5 F charge, **2a** was obtained in 46%. Increasing the charge did not lead to higher yields (Table 1, Entry 10–11). Surprisingly, the yield with the application of a current density of 5 mA/cm² in MeCN/H₂O (8 v/v%) media turned out to be superior compared to the standard conditions (Table 1, Entry 12). Interestingly, different electrode materials did not have a significant effect on the outcome of the reaction (see Supporting Information).

Based on our findings, the scope was further extended with both mono- and polyunsaturated monoterpenes with the presence of different functional groups (Scheme 2). Structurally challenging cyclic, linear monoterpenes, terpenoids and phenylpropanoids were subjected to the optimized conditions by varying the amount of charge to obtain their dibrominated derivatives. Among all the terpenes tested, the cyclic monoterpenoid, carvone went readily under electrochemical bromination to **3** with an isolated yield of 82%. Similarly, peril-



Scheme 2. Scope for the synthesis of dibrominated derivatives. Reaction conditions: Substrate (0.7 mmol), NaBr (2.1 mmol), MeCN/H₂O (5 mL, 8 v/v%), glassy carbon electrodes, undivided cell, constant current, $j = 5 \text{ mA}/\text{cm}^2$, 1.5–5.5 F, 30 °C. [a] Yields determined by ¹H NMR (internal standard: CH₂Br₂). Isolated yields are in brackets. gC = glassy carbon. [*] Diastereomeric ratio was postulated from the crystallographic data and d.r. of **2b**.

aldehyde and 4-allylanisole showed great selectivity to give **4** and **9** with an isolated yield of 65% and 56% respectively. In the presence of an electron-withdrawing group the yields were generally higher. This could be attributed to the fact that electron-withdrawing groups in the vinylic position reduces the nucleophilicity of the given alkene and it is less susceptible to side reactions. The effect was also observed, that in the case of such terpenes and terpenoids (e.g. carvone and perillaldehyde) bromination was observed on the terminal alkene which is less nucleophilic by electronic means. The method proved to be applicable for a wide range of natural terpenes and terpenoids including various functional groups such as ketones, aldehydes and alcohols with good to high yields and great selectivity.

Subsequently, the scalability of the reaction was studied. To demonstrate, the synthesis of **3** was scaled up from 0.7 mmol to 3.5 mmol (5-fold scale-up) in a 25 mL PTFE undivided cell (Figure 1). However, the reaction showed a slightly decreased yield of 72%.

By adjusting the reaction parameters and the cell geometry, the reaction selectivity could be inverted to favor the formation

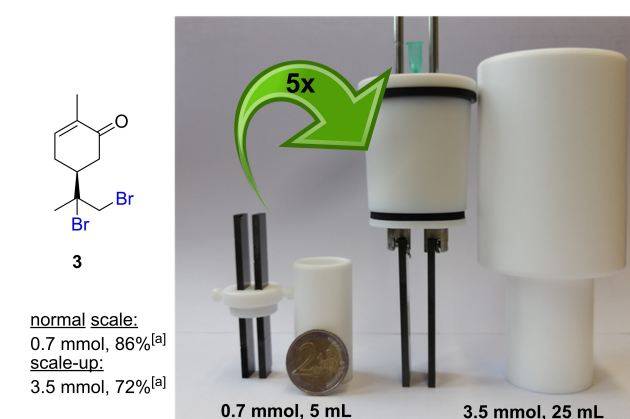
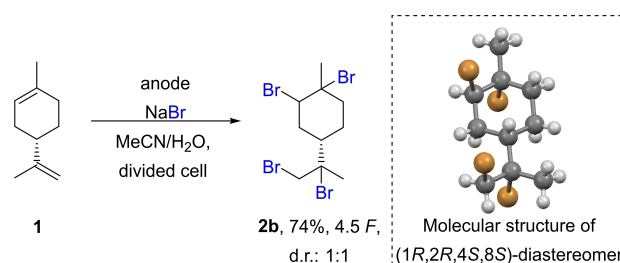


Figure 1. Scale-up reaction. Comparison between screening cell and scale-up cell. A two-euro coin is included for size comparison. [a] ¹H NMR yields (internal standard: CH₂Br₂).

of **2b**. As carbon-halogen bonds are prone to cathodic lability, a PTFE divided cell with glass frit membrane was employed.^[54] Via applying an increased amount of charge, **2b** were obtained with an isolated yield of 74%. Upon crystallization of **2b** only crystals from (1*R*,2*R*,4*S*,8*S*)-diastereomer were obtained (Scheme 3) (see Supporting Information).

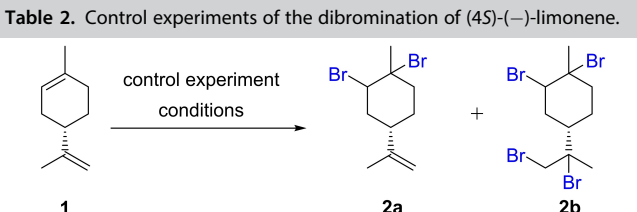
To exhibit the utility of our procedure over the conventionally available methods, dibromination of (4*S*)-(–)-limonene was carried out in the presence of elemental bromine and via a DMSO/HBr system (Table 2).^[55,56] In both cases, the desired products were obtained in diminished yields. In terms of the DMSO/HBr system, **2a** was obtained in 39% yield, however, the selectivity of the reaction was dramatically decreased (See SI for more information). The high selectivity of the electrochemical bromination method could be attributed to the slower and controlled in-situ generation of bromine during the electrolysis.

The reaction mechanism was postulated according to Scheme 4. Cyclic voltammetry studies revealed that the generation of bromine is a 2-electron-oxidation process in which bromide anions undergo oxidation to form bromine that are in equilibria with the relatively stable tribromide species. The second oxidation is accounted to the oxidation of these



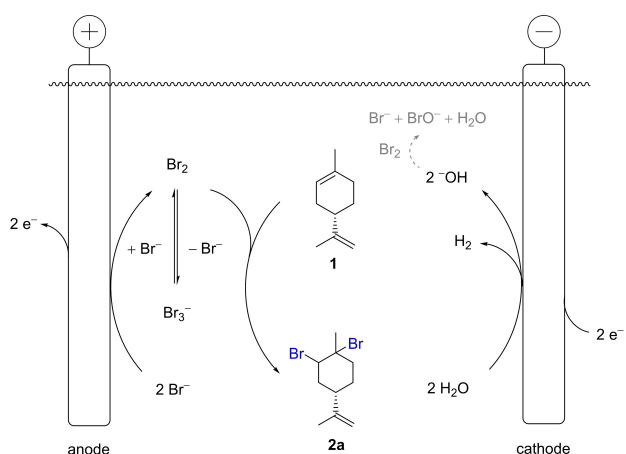
Scheme 3. Electrochemical tetrabromination of **1**. Reaction conditions: Anodic compartment: **1** (0.7 mmol), NaBr (2.1 mmol), MeCN/H₂O (5 mL, 8 v/v %). Cathodic compartment: NaBr (2.1 mmol), MeCN/H₂O (5 mL, 8 v/v%), glass frit membrane, glassy carbon electrodes, divided cell, constant current, $j = 5 \text{ mA}/\text{cm}^2$, 4.5 F, 30 °C. Isolated yield. Molecular structure of (1*R*,2*R*,4*S*,8*S*)-diastereomer of **2b** was obtained by crystallographic X-ray analysis.

Table 2. Control experiments of the dibromination of (4S)-(-)-limonene.



Conditions ^[a]	2a [%] ^[b]	2b [%] ^[b]
a) Br ₂ ^[55]	22	13
b) DMSO/HBr ^[56]	39	10
c) Electrochemical method	54	0

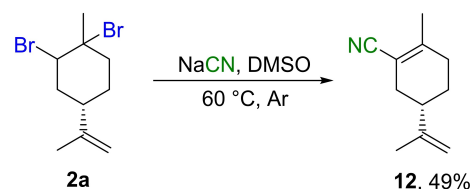
[a] Control experiments. Reaction conditions: a) Terpene (0.7 mmol), Br₂ (99.6%, 0.7 mmol), DCM (2.0 mL), 0 °C, 30 minutes. b) Terpene (0.7 mmol), DMSO (0.8 mmol), HBr (48 w/w% aq., 1.6 mmol), EtOAc (2.8 mL), 60 °C, 30 minutes. c) terpene (0.7 mmol), NaBr (2.1 mmol), MeCN/H₂O (5 mL, 8 v/v %), glassy carbon electrodes, undivided cell, constant current, *j* = 5 mA/cm², 1.5–5.5 F, 30 °C. [b] Yield determined by ¹H NMR (internal standard: CH₂Br₂).



Scheme 4. Postulated reaction mechanism for the electrochemical bromination of 1.

tribromide species to bromine, which was in accordance with previous reports.^[57–60] The electrochemical bromination is assumed to occur via the formation of the reactive bromonium ion intermediates which then undergo nucleophilic ring opening by the free bromide anions resulting in the desired products. The reaction is complemented by the cathodic reduction of water to generate hydrogen gas. This was further supported by the visual observation of gas evolution at the cathode as well as an increase of the pH value from 6 to 14 in the cathodic chamber of divided cells. In undivided cells the pH value remained constant, suggesting the formation of hypobromite.^[61]

To exhibit the multipurpose application of 1,2-vicinal dibromides as intermediates, **2a** was subjected to the well-known Kolbe nitrile method (Scheme 5).^[62] Nitrile groups are vital building blocks in organic synthesis due to their ability to be converted into multiple functional groups. Via a nucleophilic substitution and a subsequent elimination in one-pot, the α,β -unsaturated nitrile derivative **12** could be synthesized for the first time with an isolated yield of 49%.



Scheme 5. Functionalization of **2a**. Conditions: **2a** (1.0 mmol), NaCN (4.0 mmol), dimethylsulfoxide (DMSO), argon atmosphere, 60 °C, isolated yield.

Conclusion

To conclude, a safe, selective, and sustainable electrochemical bromination protocol of terpenes was established. The highlights of this approach are the utilization of NaBr that serves both as a reagent and supporting electrolyte, the use of inexpensive electricity as “green” oxidant as well as the application of sustainable carbon electrodes. This method facilitates the selective functionalization of both mono- and polyunsaturated molecules demonstrated in 10 examples with yields up to 82%. The electrochemical bromination of structurally delicate compounds has been proven to be superior towards the already existing methods. Scalability as well as further functionalization has been demonstrated.

Experimental Section

General procedure for the reactions in 5 mL undivided PTFE cells

A solution of sodium bromide (2.1 mmol) in 5.0 mL of solvent mixture constructed of acetonitrile (4.6 mL) and deionized water (0.4 mL, 8 v/v%) was transferred into an undivided 5 mL PTFE cell and warmed to 30 °C. Once the electrolysis temperature was reached, terpene (0.7 mmol) was added via a 100 μ L Hamilton syringe and electrolyzed at glassy carbon electrodes with a current density of 5 mA/cm² at 30 °C. After applying 1.5–5.5 F, the reaction solution was extracted with 15 mL ethyl acetate and 15 mL deionized water. After phase separation, the organic layer was washed two times with deionized water (15 mL), with brine, dried over magnesium sulfate and concentrated under vacuo. The product was quantified via ¹H NMR using CH₂Br₂ as internal standard. In most cases, the crude product was spectroscopically pure.

General procedure for the reactions in 5 mL divided PTFE cells

A solution of sodium bromide (2.1 mmol) in 5 mL of solvent mixture constructed of acetonitrile (4.6 mL) and deionized water (0.4 mL, 8 v/v%) was transferred into the anodic compartment of PTFE cell. The same step was repeated for the cathodic compartment. The cell is warmed to 30 °C. Once the electrolysis temperature was reached, **terpene** (0.7 mmol) was added to the anodic compartment via a 100 μ L Hamilton syringe and electrolyzed at glassy carbon electrodes. A constant current electrolysis with a current density of 5 mA/cm² was performed at 30 °C. After applying 4.5 F, the reaction solution was extracted with 15 mL ethyl acetate and

15 mL deionized water. After phase separation, the organic layer was washed two times with deionized water (15 mL), with brine, dried over magnesium sulfate and concentrated under vacuo to give the spectroscopically pure product.

General procedure for the reaction in 25 mL divided PTFE cell

A solution of sodium bromide (10.5 mmol) in 25 mL solvent mixture constructed of acetonitrile (23.0 mL) and deionized water (2.0 mL, 8 v/v%) was transferred into an undivided 25.0 mL PTFE cell warmed to 30 °C. Once the electrolysis temperature was reached, terpene (3.5 mmol) was added via a 500 μ L Hamilton syringe and electrolyzed at glassy carbon electrodes. A constant current electrolysis with a current density of 5 mA/cm² was performed at 30 °C. After applying 3.0 F, the reaction solution was extracted with 80 mL ethyl acetate and 80 mL deionized water. After phase separation, the organic layer was washed two times with deionized water (80 mL), with brine, dried over magnesium sulfate and concentrated under vacuo. The product was quantified by ¹H NMR using CH₂Br₂ as internal standard.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Alkenes · Bromine · Electrochemistry · Halogenation · Renewable resources

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