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Research Article

Catalytic β-Bromohydroxylation of Natural Terpenes: Useful Intermediates for the Synthesis of Terpenic Epoxides

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In a one-step procedure, various β-bromoalcohols were synthesized from natural terpenes in good to excellent yields. Using different catalysts, the reaction was carried out at room temperature, with H_2O as nucleophile and *N*-bromosuccinimide as a bromine source under mild reaction conditions. The synthesized β-bromoalcohols were subsequently converted in situ to the corresponding epoxides in good yields.

1. Introduction

Terpenes, the major constituents of essential oils, present a class of natural products which are cheap and abundantly available. This pool of chiral substances can be transformed into valuable substances of considerable interest mostly for the industrial production of pharmaceuticals, cosmetics, fragrances, perfumes, and flavors, besides useful synthetic intermediates and chiral building blocks [1].

There is a vast literature on catalytic transformations of terpenes for a broad variety of purposes. These transformations include isomerization, oxidation, hydration, condensation, hydroformylation, hydrogenation, cyclization, rearrangement, and ring contraction or enlargement [2–4]. Among these, halogenation, co-halogenation, and epoxidation being relatively inexpensive are the preferred methods for the large-scale production of flavor chemicals [5]. On the other hand, vic-bromoalcohols are extremely versatile building blocks in synthetic organic and industrial chemistry and are widely used for the preparation of marine natural products and other biologically valuable substances [6–9]. In addition, due to their high reactivity, these compounds can be utilized for some useful synthetic transformations such as ketones [10–12], aldehydes [13], epoxides [14, 15], and other derivatives [16].

The preparation of β-bromoalcohols has been reported directly from simple olefins by reaction with *N*-bromosuccinimide (NBS), which is a better choice compared to hazardous molecular halogens and other brominating agents, using several catalysts such as ionic liquids [17], β-cyclodextrin as a supramolecular catalyst [18], diphenyldiselenide (PhSeSePh) [19], NH_4OAc [20], and iodine [21]. A significant progress has been made in recent years regarding vicinal hydroxybromination of alkenes and their subsequent functionalization. However, limited examples using terpenes as a material source have been reported.

Recently, we have described an efficient process for the preparation of vic-aminoalcohols directly from simple alkenes in good yields [22]. Our approach is based initially on the preparation of bromoalcohols by treating the corresponding alkenes at room temperature in the presence of NBS as a source of bromine and a catalytic amount of SiO_2 in water, followed by in situ addition of amine to form aminoalcohols. In our efforts to develop this methodology and

to continue with our interest in the valorization of natural terpenes [23–27], we report here an expanded study of this process to natural terpenes. The scope and limitations of these transformations are discussed.

2. Experimental

2.1. Characterization and Methods. NMR studies were performed on Bruker Avance 300 and Bruker Avance DRX 400 spectrometers in $CDCl_3$, chemicals shifts are given in ppm relative to the solvent $CDCl_3$ (7.27 ppm (^{1}H); 77.0 ppm (^{13}C)), and coupling constants (*J*) are given in Hz. ATR-IR spectra were measured using a Bruker Alpha with diamond ATR accessory. Mass spectrograms were recorded on a Thermo Electron MAT 95-XP spectrometer. The reaction mixtures were analyzed on a Shimadzu GCMS-QP 2010 chromatograph equipped with an FID and an MS detector and Optima 5MS column (50 m × 0.32 mm × 0.5 μm).

The parameters of the GC program were injector 250°C and FID 320°C; the temperature ramp started at 60°C for 3 min, then it was raised with 10°C/min up to 160°C and with 5°C/min up to 260°C. It was left at 260°C for 7 min; column pressure 138.8 kPa, column flow 3.02 mL/min; linear velocity 39.5 cm/s; total flow 50.7 mL/min. Conversion and yield were calculated using dodecane as the internal standard. Analytical thin layer chromatography (TLC) was conducted on Merck aluminium plates 60 F-254 with 0.2 mm layer of silica gel. Most reagents and solvents used in the experiments were purchased from commercial sources. SiZr30, Ti-SBA 15, and SBA 15 were synthesized according to literature procedures [28].

2.2. General Procedure for Bromohydroxylation of Terpenes. In a typical experiment, *N*-bromosuccinimide (1.3 equiv.) and 0.04 g of catalyst were added to a vigorously stirred solution of terpene (0.4 g) in aqueous acetone (4 : 1, v/v). The mixture was stirred at room temperature for 15 min. The reaction was monitored by GC. At the end of the reaction, the mixture was diluted with water and extracted three times with EtOAc (10 mL). The organic layer was dried over Na_2SO_4 and then concentrated, and the residue was purified by column chromatography using silica gel with EtOAc-heptane (3 : 7, v/v) as eluent. The obtained pure bromoalcohols were characterized by mass spectrometry, ATR-IR, MS/ESI measurements, and NMR spectroscopy. Characterization data can be found in ESI.

2.3. General Procedure for In Situ Synthesis of Epoxides. First, the respective bromoalcohols were prepared by the method described above. Then, in the same reactor, two equivalents of amine were added and the resulted mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Pure epoxide was obtained by column chromatography over silica gel using a mixture of EtOAc-heptane (2 : 8, v/v) and characterized by mass spectrometry, ATR-IR, MS/ESI measurements, and NMR spectroscopy. Characterization data can be found in ESI.

The structures of **2a** and **3a** were confirmed by comparison with literature data [29] and an authentic sample.

6-Bromo-3,7-dimethyl-octane-1,7-diol **2b** (mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.88, 0.90 (3H, 2d, J = 6.3 and 6.5 Hz, CH_3), 1.31 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.34–1.77 (6H, m, 3 × CH_2), 1.83–2.00 (1H, m, CH), 2.43 (2H, broad s, OH), 3.65 (2H, m, CH_2), 3.95 (1H, 2 dd, J = 11.3 and 2.0 Hz, CH); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.21, 19.91 (C3-CH_3), 25.99, 26.14 and 26.24, 26.39 (gem-dimethyl), 28.67, 28.90 (C3), 31.13, 31.21 (C5), 35.71, 36.03 (C4), 38.95, 39.83 (C2), 60.57 (C1), 71.09, 71.25 (C6), 72.54, 72.60 (C7); ATR-IR: $\tilde{\nu}$ = 3348, 2952, 2927, 2872, 1459, 1378, 1131, 1052, 774, 624 cm^{-1}; MS (EI, *m*/*z* (%)): 176 (3), 121 (2), 97 (6), 70 (12), 59 (100), 41 (10); MS (ESI, 180 eV): $[M + Na]^+$ 275.06135, 277.05987 calc. 275.06171, 277.05974; $C_{10}H_{21}BrO_2$ (253.18).

6,7-Epoxy-3,7-dimethyl-1-octanol **3b** (mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.851, 0.853 (3H, 2 d, J = 6.5 and 6.4 Hz, CH_3), 1.20 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.27–1.38 (2H, m, CH_2), 1.38–1.61 (5H, m, 2 CH_2 and CH), 2.48, 2.55 (1H, broad, OH), 2.65 (1H, t, J = 6.0 Hz, CH), 3.58 (2H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 18.45, 18.50 and 19.29, 19.44 (gem-dimethyl), 24.70 (C3-CH_3), 25.99, 26.21 (C5), 29.04, 29.23 (C3), 33.48, 33.50 (C4), 39.35, 39.59 (C2), 58.30, 58.41 (C7), 60.43 (C1), 64.54, 64.59 (C6); ATR-IR: $\tilde{\nu}$ = 3396, 2958, 2925, 2871, 1459, 1378, 1057, 676 cm^{-1}; MS (EI, *m*/*z* (%)): 111 (3), 85 (22), 71 (31), 59 (100), 55 (52), 41 (42); MS (ESI, 180 eV): $[M + H]^+$ 173.15374, calc. 173.15361, $[M + Na]^+$ 195.13595, calc. 195.13555; $C_{10}H_{20}O_2$ (172.27).

6-Bromo-3,7-dimethyl-oct-2-ene-1,7-diol **2c**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.30 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.68–1.86 (1H, m, 1H of CH_2), 1.97–2.18 (2H, m, CH_2), 2.25–2.38 (1H, m, 1H of CH_2), 2.69, 2.79 (2H, 2 broad, OH), 3.90 (1H, dd, J = 1.7 and 11.6 Hz, CH), 4.10 (2H, d, J = 6.9 Hz, CH_2), 5.42 (1H, t, J = 6.6 Hz, CH); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 16.13 (C3-CH_3), 25. 84 and 26.41 (gem-dimethyl), 31.45 (C5), 37.68 (C4), 58.80 (C1), 69.12 (C6), 72.45 (C7), 124.58 (C2), 137.34 (C3); ATR-IR: $\tilde{\nu}$ = 3401, 2975, 2932, 2873, 1713, 1450, 1367, 1133, 1063, 818 cm^{-1}; MS (EI, *m*/*z* (%)): 153 (4), 135 (48), 119 (8), 109 (15), 93 (25), 71 (38), 68 (100), 43 (76), 41 (49); MS (ESI, 180 eV): $[M + H]^+$ 251.06357, calc. 251.06393; $C_{10}H_{19}BrO_2$ (250.05).

6,7-Epoxy-3,7-dimethyl-oct-2-en-1-ol **3c**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.16 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.50–1.63 (2H, m, CH_2), 1.58 (3H, s, CH_3), 1.98–2.15 (2H, m, CH_2), 2.62 (1H, t, J = 6.2 Hz, CH), 2.86 (1H, broad, OH), 4.02 (2H, d, J = 6.6, CH_2), 5.33 (1H, t of q, J = 6.8, 1.2, =CH); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 15.93 and 18.43 (gem-dimethyl), 24.54 (C3-CH_3), 26.79 (C5), 35.95 (C4), 58.31 (C7), 58.61 (C1), 63.88 (C6), 124.13 (C2), 137. 36 (C3); ATR-IR: $\tilde{\nu}$ = 3397, 2961, 2924, 2872, 1668, 1447, 1378, 998, 676 cm^{-1}; MS (EI, *m*/*z* (%)): 152 (1), 137 (3), 119 (2), 109 (19), 85 (63), 81 (84), 59 (88), 41 (100); MS (ESI, 180 eV): $[M + H]^+$ 171.13767, calc. 171.13796, $[M + Na]^+$ 193.11975, calc. 193.11990; $C_{10}H_{18}O_2$ (170.25).

5-(1-(Bromomethyl)-1-hydroxyethyl)-2-methylcyclohex-2-en-1-one **2d** (mixture of diastereomers). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.15 (3H, s, CH_3), 1.59 (3H, s, CH_3), 2.03–2.51 (5H, m, $2\times CH_2$, CH), 3.22–3.39 (3H, m, OH and CH_2Br), 6.59–6.70 (1H, m, =CH); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 15.17 (C2-CH_3), 22.12, 22.45 (C7-CH_3), 25.81, 26.72 (C4), 37.92, 38.70 (C6), 41.36, 41.50 (C5), 41.86, 42.14 (C8), 71.51, 71.60 (C7), 134.44, 134.61 (C2), 144.86, 145.48 (C3), 199.69, 199.94 (C1=O); ATR-IR: $\tilde{\nu}$ = 3428, 2975; 1655; 1369; 1105; 960; 655 cm^{-1}; MS (EI, *m*/*z* (%)): 230 (6), 228 (6), 153 (12), 137 (29), 121 (8), 110 (100), 95 (71), 81 (30), 57 (29), 41 (21); MS (ESI, 180 eV): $[M+H]^+$ 247.03314, calc. 247.03345; $C_{10}H_{15}BrO_2$ (246.13).

2-Methyl-5-(2-methyloxiranyl)-cyclohex-2-enone **3d** (mixture of diastereomers). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.21–1.26 (3H, m, CH_3-C-O), 1.66–1.71 (3H, m, CH_3-C=C), 1.94–2.23 (3H, m, CH_2 + CH), 2.27–2.39 (1H, m, 1H of CH_2), 2.42–2.54 (2H, m, CH_2), 2.57–2.64 (1H, m, 1H of CH_2), 6.63–6.70 (1H, m, =CH); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 15.44 (C2-CH_3), 18.20, 18.71 (C7-CH_3), 27.51, 27.70 (C4), 39.70, 40.08 (C6), 40.56, 41.08 (C5), 52.22, 52.62 (C8), 57.63, 57.73 (C7), 135.27, 135.32 (C2), 143.73, 143.96 (C3), 198.51, 198.56 (C1=O); MS (EI, *m*/*z* (%)): 151 (4), 148 (8), 133 (19), 123 (19), 109 (100), 108 (90), 91 (40), 82 (57), 67 (19), 54 (47), 39 (40); MS (ESI, 180 eV): $[M+H]^+$ 167.10734, calc. 167.10725; $C_{10}H_{15}BrO_2$ (166.21).

6-Bromo-7-hydroxy-3,7-dimethyl-octan-1-al **2e**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.90–0.96 (3H, m, CH_3), 1.29 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.23–1.47 (1H, m, 1H of CH_2), 1.50–1.76 (2H, m, CH + 1H of CH_2), 1.82–1.98 (1H, m, 1H of CH_2), 1.99–2.12 (1H, m, 1H of CH_2), 2.15–2.43 (2H, m, CH_2), 3.87–3.92 (2H, m, OH and Br-CH), 9.70 (1H, s, CHO); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.29, 19.99 (C3-CH_3), 26.06, 26.15 and 26.25, 26.36 (gem-dimethyl), 27.19, 27.60 (C3), 31.00, 31.18 (C5), 35.56, 35.84 (C4), 50.34, 51.05 (C2), 70.45, 70.54 (C6), 72.49, 72.52 (C7), 202.57, 202.64 (CHO); ATR-IR: $\tilde{\nu}$ = 3412, 2959, 2931, 2725, 1715, 1460, 1380 cm^{-1}; MS (EI, *m*/*z* (%)): 192 (4), 153 (4), 109 (8), 95 (10), 71 (42), 59 (100), 43 (33), 41 (17); MS (ESI, 180 eV): $[M+H]^+$ 251.06462, 253.06248, calc. 251.06412, 253.06215; $C_{10}H_{19}BrO_2$ (251.16).

6,10-Dimethyl-9,10-epoxy-undec-3-en-2-one **3e** (mixture of diastereomers). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.87, 0.92 (3H, 2d, J = 6.7 Hz, CH_3), 1.20 (3H, s, CH_3), 1.24 (3H, s, CH_3), 1.27–1.70 (5H, m, CH, $2\times CH_2$), 1.96–2.27 (2H, m, CH_2), 2.18 (3H, s, CH_3), 2.62 (1H, t, J = 5.9 Hz, CH-O), 6.01 (*trans*), 6.26 (*cis*) (1H, 2 d, J = 15.8 and 15.3 Hz, =CH-C=O), 6.64–6.88 (1H, m, -CH =); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 18.48, 18.53 and 19.36, 19.40 (gem-dimethyl), 24.70 (C6-CH_3), 26.19, 26.22 (C8), 26.27, 26.74 (C6), 32.28, 32.37 (C1), 33.17, 33.33 (C7), 39.78, 39.94 (C5), 58.00, 58.10 (C10), 64.15, 64.20 (C9), 129.87, 132.42 (C3), 146.14, 146.63 (C4), 198.26 (CHO); ATR-IR: $\tilde{\nu}$ = 2959, 2925, 2873, 1672, 1626, 1459, 1378, 1252,980 cm^{-1}; MS (EI, *m*/*z* (%)): 152 (2), 137 (12), 124 (6), 109 (29), 95 (49), 81 (40), 67 (24), 43 (100), 41 (39); MS (ESI, 180 eV): $(M+H)^+$ 211.16921, calc. 211.16926; $C_{13}H_{22}O_2$ (210.31).

6-Bromo-7-hydroxy-3,7-dimethyl-oct-2-en-1-al **2f** (mixture of diastereomers). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 1.20–1.59 (1H, m, 1H of CH_2), 1.36 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.66–1.84 (1H, m, 1H of CH_2), 1.84–2.24 (1H, m, 1H of CH_2), 1.99, 2.196 (3H, 2d, J = 1.3 and 1.2 Hz, CH_3C =), 2.24–2.45 (1H, m, 1H of CH_2) 2.56–3.03 (1H, m, 1H of CH_2) 3.89–4.07 (2H, m, OH and Br-CH), 5.90–5.97 (1H, m, =CH), 10.00, 10.02 (1H, 2d, J = 7.8 and 7.6 Hz, CHO); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 17.70 (C3-CH_3), 24.73, 26.26 and 26.38, 26.61 (gem-dimethyl), 31.42, 32.48 (C5), 39.17 (C4), 68.76, 69.02 (C6), 72.48, 72.51 (C7), 127.71, 129.45 (C2), 162.92, 162.02 (C3), 190.76, 191.13 (CHO); MS (EI, *m*/*z* (%)): 151 (12), 133 (6), 123 (7), 109 (7), 84 (86), 59 (100), 43 (46), 41 (28); $C_{10}H_{17}BrO_2$ (249.15); MS (ESI, 180 eV): $[M+H]^+$ 249.04866, calc. 249.04802; $C_{10}H_{15}BrO_2$ (248.15).

3. Results and Discussion

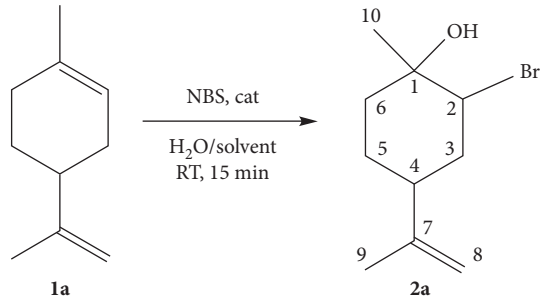
*3.1. Synthesis of Bromoalcohol **2a**.* In connection with our ongoing effort to prepare aminoalcohols from terpenes, we first focused on the optimization of bromohydrin synthesis to improve published results regarding limonene substrates. In general, it is a reaction that proceeds at a yield of 70–87% [29, 30]. Hence, we studied bromohydroxylation of limonene **1a** under various reaction conditions (Scheme 1).

Limonene **1a**, which contains two different double bonds, was mainly bromohydroxylated to **2a** at the internal double bond, while the external double bond remained unchanged (Table 1). The reaction proceeded smoothly at room temperature under extremely mild conditions. Systematic investigation in the presence of various catalytic systems was undertaken to define the best reaction conditions.

As depicted in Table 1, among the catalysts studied, CeO_2 nanopowder and Dowex Marathon A, Cl^- form, appeared to be the most suitable (entries 11, 12). They produced **2a** in 70% yield within 15 min. But the differences in conversion and yield were not so significant whether acidic or basic catalysts were used. Probably, the generation of electrophilic bromine species forming halonium ion intermediates with the terpene followed by the nucleophilic attack of H_2O was possible at all polar catalyst surfaces. The most efficient catalyst (Dowex Marathon A) was subsequently used for the next steps of the optimization.

The effect of NBS was also evaluated (Table 2). Hence, the increase of NBS amount had a boosting effect on the conversion of **1a**. When it was treated with at least 1.7 equivalents of NBS in an aqueous solution of acetone, **1a** was totally converted (entries 7, 8). However, the maximum yield of the corresponding bromoalcohol **2a** (70%) was obtained with only a slight surplus of NBS (1.3 equiv.) (entry 3). Using a larger excess, various by-products coming probably from side reactions (bromohydroxylation of exo-double bond) during the formation of bromohydrin were detected by gas chromatography.

The yield of bromoalcohol **2a** could be also influenced by the nature of the solvent (Table 3). As can be seen in Table 3, the highest efficient protocol was achieved in acetone, methanol DMSO and THF (entries 1–5). In nitromethane, acetonitrile, and dichloroethane less than 50% yield was obtained (entries 6–8). An improvement of conversion and yield was achieved in acetone by lowering the reaction temperature to 0°C (entry 2). The reaction of **1a** with NBS in



Scheme 1: Synthesis of limonene bromoalcohol.

Table 1: Influence of the catalyst on the bromohydroxylation of **1a**.

Entry	Catalyst	Remarks	Conversion (%)	Yield of **2a** (%)
1	SiO_2	60 Å, 70–230 mesh	79	64
2	SIRAL 1	Al_2O_3/SiO_2 99 : 1, 280 m^2/g	81	65
3	Aerosil 300	SiO_2, 300 m^2/g	87	51
4	SiZr30	$SiO_2/ZrO_2 = 30$, 573 m^2/g	85	62
5	Zeolite beta, H^+ form	ZEO cat PBH, SiO_2/Al_2O_3 25–60, 600 m^2/g	83	57
6	Ti-SBA15	$SiO_2/TiO_2 = 30$, 668 m^2/g	78	61
7	SBA 15	SiO_2, 850 m^2/g	82	62
8	TiO_2	Hombikat UV 100 (anatase), 250 m^2/g	81	50
9	Zeolite Y, H^+ form	CBV 720 (Zeolyst), $SiO_2/Al_2O_3 = 30$, 780 m^2/g,	86	55
10	ZrO_2	Monoclinic phase, (Alfa Aesar), 90 m^2/g	81	66
11	CeO_2	Nanopowder (Aldrich), particle size ≤ 25 nm	82	70
12	Dowex Marathon A	Cl^- form (Aldrich), 1.3 meq/mL,	76	70
13	Montmorillonite K-10	Powder, (Aldrich), 250 m^2/g	84	58
14	None		60	40

Reaction conditions: limonene 0.4 g, NBS 1.3 equiv., catalyst 0.04 g, 5 mL acetone/H_2O 4 : 1 (v/v), r.t., 15 min. Conversion and yield were calculated by GC analysis using dodecane as the internal standard.

Table 2: Effect of NBS amount on bromohydroxylation of **1a**.

Entry	NBS (equiv.)	Conversion (%)	Yield of **2a** (%)
1	1	61	54
2	1.1	69	56
3	1.3	76	70
4	1.4	89	67
5	1.5	95	68
6	1.6	98	68
7	1.7	100	57
8	2	100	43

Reaction conditions: **1a** 0.4 g, NBS, catalyst (Dowex Marathon A, Cl^- form) 0.04 g, 5 mL acetone/H_2O 4 : 1 (v/v), r.t., 15 min. Conversion and yield were calculated by GC using dodecane as the internal standard.

Table 3: Solvent effect on the bromohydroxylation of **1a**.

Entry	Solvent	Conversion (%)	Yield of **2a** (%)
1	Acetone	76	70
2	Acetone[a]	89	82
3	MeOH	88	79[b]
4	DMSO	84	63
5	THF	80	63
6	Nitromethane	75	26
7	Acetonitrile	72	49
8	Dichloroethane	55	23

Reaction conditions: **1a** 0.4 g, NBS 1.3 equiv., catalyst (Dowex Marathon A, Cl^- form) 0.04 g, 5 mL solvent/H_2O 4 : 1 (v/v), r.t., 15 min; [a]at 0°C; [b]formation of 2-bromo-1-methoxy-1-methyl-4-(1-methylethenyl)-cyclohexane. Conversion and yield were calculated by GC using dodecane as the internal standard.

methanol led selectively to the corresponding bromomethoxylated product in good yield (entry 3).

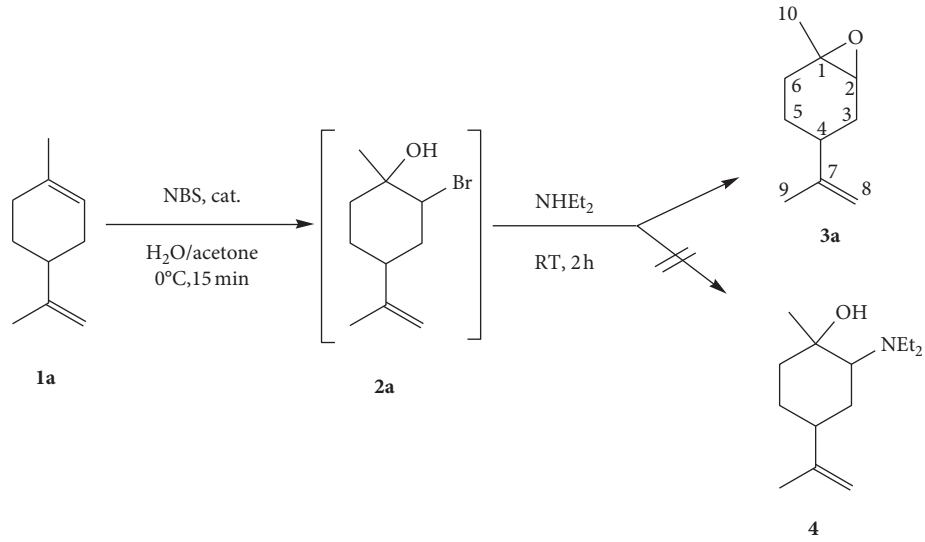
Subsequently, the influence of the catalyst amount was also studied (Table 4). The best result was achieved with catalyst/substrate ratio of 1 : 10 (w/w; entry 2). Under high ratio the yield decreased probably due to the formation of by-products resulting from consecutive reactions (entries 3, 4).

*3.2. In Situ Addition of Amines to β-Bromoalcohol **2a**.* The aim of this reaction sequence was the synthesis of vicinal limonene aminoalcohol in one-pot procedure via

Table 4: Influence of the catalyst amount on the bromohydroxylation of **1a**.

Entry	Catalyst (g)	Conversion (%)	Yield of **2a** (%)
1	0.03	89	67
2	0.04	89	82
3	0.06	81	65
4	0.08	77	61
5	None	60	40

Reaction conditions: **1a** 0.4 g, NBS 1.3 equiv., catalyst (Dowex Marathon A, Cl^- form), 0.04 g, acetone/H_2O 4 : 1 (v/v), 15 min. Conversion and yield were generally calculated by GC analysis using dodecane as the internal standard.



Scheme 2: Synthesis of epoxide **3a** via bromohydrin.

Table 5: Amine effect on the synthesis of epoxide **3a**.

Entry	Amine	Conversion (%)	Yield of **3a** (%)
1	Aniline	50	0
2	Diethylamine[a]	92	82
3	Diethylamine[b]	90	87
4	1-Phenylethylamine	71	38
5	1-Phenylethylamine[c]	69	31
6	Morpholine	94	48
7	Ammonia	90	33

Reaction conditions: **1a** 0.4 g, NBS 1.3 equiv., amine 2 equiv., catalyst (Dowex Marathon A, Cl^- form) 0.04 g, 5 mL acetone/H_2O 4 : 1 (v/v), r.t., 15 min; [a]2 equiv. of diethylamine; [b]3 equiv. of diethylamine; [c] reaction with THF instead of acetone. Conversion and yield were calculated by GC using dodecane as the internal standard.

β-bromoalcohol under optimized conditions (e.g. **4**, Scheme 2). Therefore, β-bromoalcohol **2a** formed in situ was treated by different amines as nucleophiles (Table 5). However, the epoxide **3a** was obtained instead of the desired aminoalcohol in spite of increasing the amount of amine. The added amine acts as a base in the HBr elimination to afford the oxirane ring [31].

As seen in Table 5, the use of aniline did not lead to any target product, neither to vic-aminoalcohol nor to the epoxide (entry 1). This study shows that diethylamine is the best base both in acetone or THF as solvent (entries 2, 3). When the less basic and more bulky phenylethylamine was used, the yield decreased, and only 38% of **3a** was obtained (entry 4). It should be noted that in the case of phenylethylamine and aniline, the formation of the respective Schiff base of acetone was observed. In order to avoid this undesired competitive reaction, the conversion was carried out in THF. Then, azomethines were not found any longer. However, in the case of phenylethylamine, both conversion of **1a** and yield of epoxide **3a** decreased (entry 5).

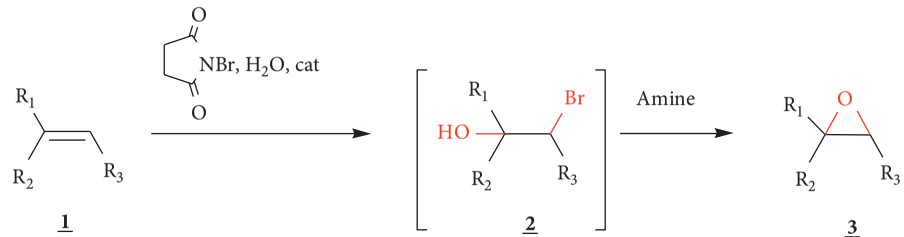
3.3. Bromohydroxylation and Epoxidation of Further Terpenes. After optimization of reaction conditions using limonene, and to assess the scope and limitation of the reaction, we extended this methodology to a variety of natural terpenes such as citronellol, geraniol, carvone, citronellal, citral, and α- and β-pinene.

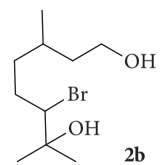
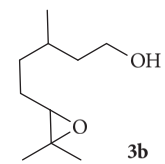
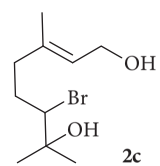
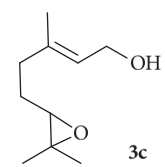
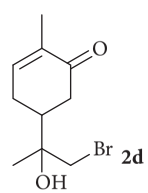
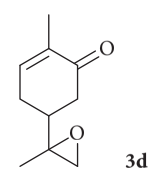
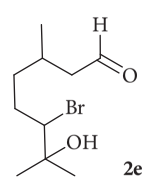
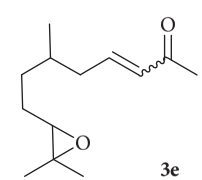
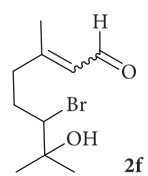
In a first series of experiments, the terpenes **1b**–**1f** were converted to the corresponding β-bromoalcohols **2b**–**2f** in very good yields (Table 6). In the case of geraniol **1c**, carvone **1d**, or citral **1f**, the allylic hydroxy or carbonyl group prevented the bromohydroxylation at the neighbouring double bond. In contrast to limonene **1a**, the double bond of the isopropenyl group reacted selectively. The products were isolated and purified by column chromatography and analytically characterized (see ESI). Afterwards, the in situ procedure optimized for limonene was applied to the other terpenes. Two equivalents of diethylamine were added to the reaction mixtures containing the intermediary bromoalcohols **2b**–**2f**, which were converted to the corresponding epoxides after 2 h. In the case of bromoalcohol **2e**, an aldol condensation between the aldehyde group and the solvent acetone beside epoxidation was observed and led to the epoxide **3e**. α- and β-pinene did not react under the optimized conditions even after 24 hours. The gas chromatogram documented the formation of a variety of products with small peak areas resulting from isomerization of the pinenes.

4. Conclusion

The catalytic synthesis of β-bromoalcohols of different terpenes succeeded via smooth reaction using NBS and H_2O as the nucleophile. The in situ treatment of these bromoalcohols with a variety of amines did not lead surprisingly to the expected vicinal aminoalcohols, but to the corresponding epoxides. The formed bromoalcohols underwent rapid dehydrohalogenation by the amine which played the role of base. We were subsequently able to isolate several epoxides in good yields. The synthesized β-bromoalcohols of natural terpenes can serve as an easily accessible platform for further structural elaboration.

Table 6: Bromohydroxylation and epoxidation of natural terpenes.



Entry		Terpenes **1b–1f**	Bromoalcohols **2b–2f**	Isolated yield **2b–2f** (%)	Epoxides **3b–3d**	Isolated yield **3b–3d** (%)
1	**1b**	R_1: CH_3 R_2: CH_3 R_3: 5-hydroxy-3-methylpentyl	 **2b**	93	 **3b**	70
2	**1c**	R_1; CH_3 R_2: CH_3 R_3: 5-hydroxy-3-methylpent-3-enyl	 **2c**	78	 **3c**	60
3	**1d**	R_1: CH_3 R_2: 4-methyl-5-oxocyclohex-3-enyl R_3: H	 **2d**	80	 **3d**	60
4	**1e**	R_1: CH_3 R_2: CH_3 R_3: 3-methyl-5-oxopentyl	 **2e**	64	 **3e**	65
5	**1f**	R_1: CH_3 R_2: CH_3 R_3: 3-methyl-5-oxopent-3-enyl	 **2f**	50	—	

Reaction conditions: terpene 0.4 g, NBS 1.3 equiv.; diethylamine 2 equiv., catalyst (Dowex Marathon A, Cl^- form) 0.04 g, 5 mL acetone/H_2O 4 : 1 (v/v), r.t.

Data Availability

NMR spectra of synthesized terpene derivatives and the device types used for recording spectra and other analytical data used to support the findings of this study are included within the supplementary materials.

Conflicts of Interest

The authors confirm that this article content have no conflicts of interest.

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Supplementary Materials

Figure S1: ^{1}H NMR spectrum of 6-bromo-3,7-dimethyl-octane-1,7-diol (bromoalcohol from citronellol) **2b**. Figure S2: ^{13}C NMR spectrum of 6-bromo-3,7-dimethyl-octane-1,7-diol (bromoalcohol from citronellol) **2b**. Figure S3: ^{1}H NMR spectrum of 6,7-epoxy-3,7-dimethyl-1-octanol (citronellol epoxide) **3b**. Figure S4: ^{13}C NMR spectrum of 6,7-epoxy-3,7-dimethyl-1-octanol (citronellol epoxide) **3b**. Figure S5: ^{1}H NMR spectrum of 6-bromo-3,7-dimethyl-oct-2-ene-1,7-diol (bromoalcohol from geraniol) **2c**. Figure S6: ^{13}C NMR spectrum of 6-bromo-3,7-dimethyl-oct-2-ene-1,7-diol (bromoalcohol from geraniol) **2c**. Figure S7: ^{1}H NMR spectrum of 6,7-epoxy-3,7-dimethyl-oct-2-en-1-ol (geraniol epoxide) **3c**. Figure S8: ^{13}C NMR spectrum of 6,7-epoxy-3,7-dimethyl-oct-2-en-1-ol (geraniol epoxide) **3c**. Figure S9: ^{1}H NMR spectrum of 5-(1′-(bromomethyl)-1′-hydroxyethyl)-2-methylcyclohex-2-en-1-one (bromoalcohol from carvone) **2d**. Figure S10: ^{13}C NMR spectrum of 5-(1′-(bromomethyl)-1′-hydroxyethyl)-2-methylcyclohex-2-en-1-one (bromoalcohol from carvone) **2d**. Figure S11: ^{1}H NMR spectrum of 2-Methyl-5-(2-methyloxiranyl)-cyclohex-2-enone one (carvone epoxide) **3d**. Figure S12: ^{13}C NMR spectrum of 2-Methyl-5-(2-methyloxiranyl)-cyclohex-2-enone (carvone epoxide) 3d. Figure S13: ^{1}H NMR spectrum of 6-bromo-7-hydroxy-3,7-dimethyl-octan-1-al (bromoalcohol from citronellal) **2e**. Figure S14: ^{13}C NMR spectrum of 6-bromo-7-hydroxy-3,7-dimethyl-octan-1-al (bromoalcohol from citronellal) **2e**. Figure S15: ^{1}H NMR spectrum of 6,10-dimethyl-9,10-epoxy-undec-3-en-2-one **3e** (reaction product of **2e**, acetone and amine). Figure S16: ^{13}C NMR spectrum of 6,10-dimethyl-9,10-epoxy-undec-3-en-2-one **3e** (reaction product of **2e**, acetone and amine). Figure S17: ^{1}H NMR spectrum of 6-bromo-7-hydroxy-3,7-dimethyl-oct-2-en-1-al (bromoalcohol from citral) **2f**. Figure S18: ^{13}C NMR spectrum of 6-bromo-7-hydroxy-3,7-dimethyl-oct-2-en-1-al (bromoalcohol from citral) **2f**. (*Supplementary Materials*)

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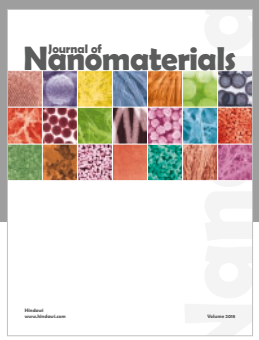

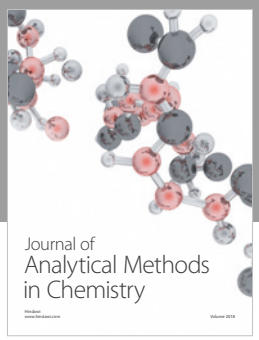

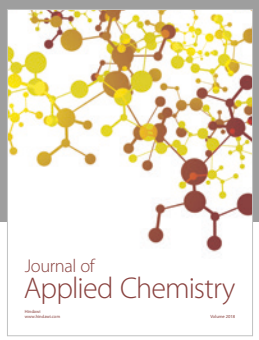

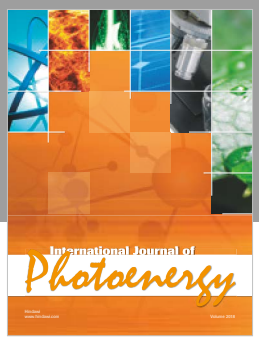

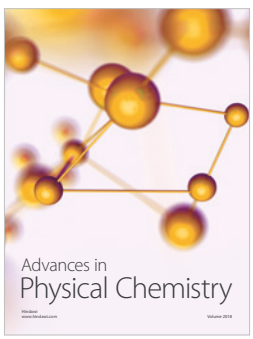

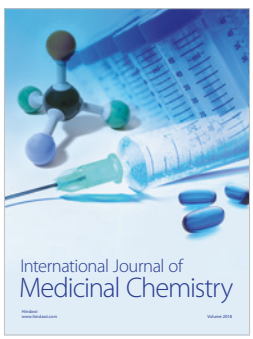

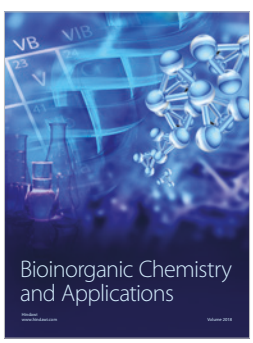

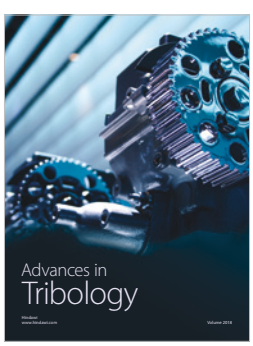

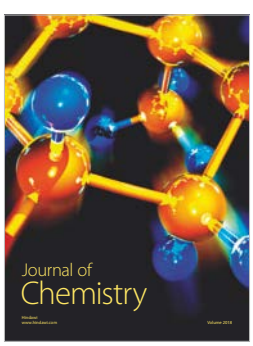

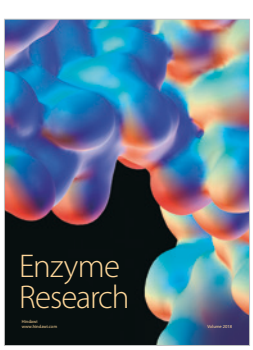

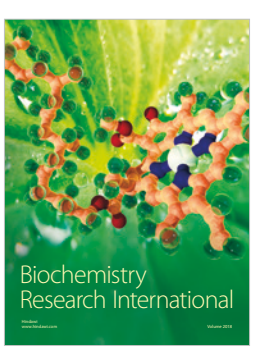

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