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INTER- AND INTRAMOLECULAR COHALOGENATION OF (*S*)-A-TERPINEOL WITH NBS

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Abstract
The reaction of (*S*)-α-terpineol with equimolar NBS in aqueous acetonitrile produced (1*R*,2*R*,4*S*)-2-bromo-4-(2-hydroxypropan-2-yl)-1-methylcyclohexanol in 75% isolated yield, along with minor amounts of (1*R*,4*S*,5*S*)-4-bromo-4,7,7-trimethyl-6-oxabicyclo[3.2.1]octane and (1*R*,4*S*,6*R*)-6-bromo-1,3,3-trimethyl-oxabicyclo[2.2.2]octane. On the other hand, the reaction performed in anhydrous acetonitrile produced the two bicyclic bromoethers as the unique products in 88% combined yield. Similar results were obtained with the reaction performed in aqueous THF (bromohydrin, bicyclic bromoethers and *cis*-α-terpineol oxide, derived from the bromohydrin formed) and in dry dichloromethane (only the bicyclic bromoethers formed in 50% combined yield). These isomeric bicyclic bromoethers could not be separated, as an equilibration occurs after a few minutes.

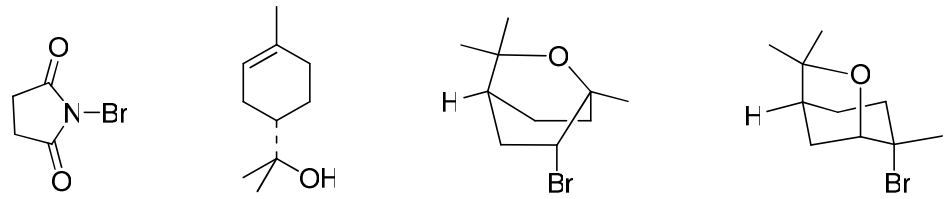
Keywords: Bromination, Reaction mechanisms, Terpenoids, Cohalogenation, Electrophilic additions

Introduction
The cohalogenation of alkenes (halogenation in the presence of a nucleophilic solvent) provides vicinal halo-functionalized products, which are useful intermediates for diverse synthetic applications.[1] The intramolecular version of the cohalogenation reaction is also known and provides functionalized cyclic products of great interest.[2] In this context, the intramolecular cohalogenation reaction of unsaturated alcohols proved to be an excellent route to obtain cyclic ethers, specially tetrahydropyrans and tetrahydrofurans.[3] When this methodology is applied to unsaturated monoterpenic alcohols, functionalized bicyclic ethers are easily obtained.[4]

N-halo compounds are versatile reagents in organic chemistry that can transfer halenium ions (X^+) to unsaturated systems (alkenes, arenes, etc).[5] Among the several *N*-halo compounds described in the literature, the *N*-bromosuccinimide (NBS) is one of the most employed due to its readily availability.[6]

The reaction of α-terpineol (**1**) with NBS/Me_2S was formerly studied by Bellesia *et al.* that reported the formation of a bromocineole of unassigned stereochemistry.[7] A few years later,

Carman and Fletcher revisited this reaction and identified a mixture of the bromotetrahydropyran (**2**) and the bromotetrahydrofuran (**3**) as the products.[8]

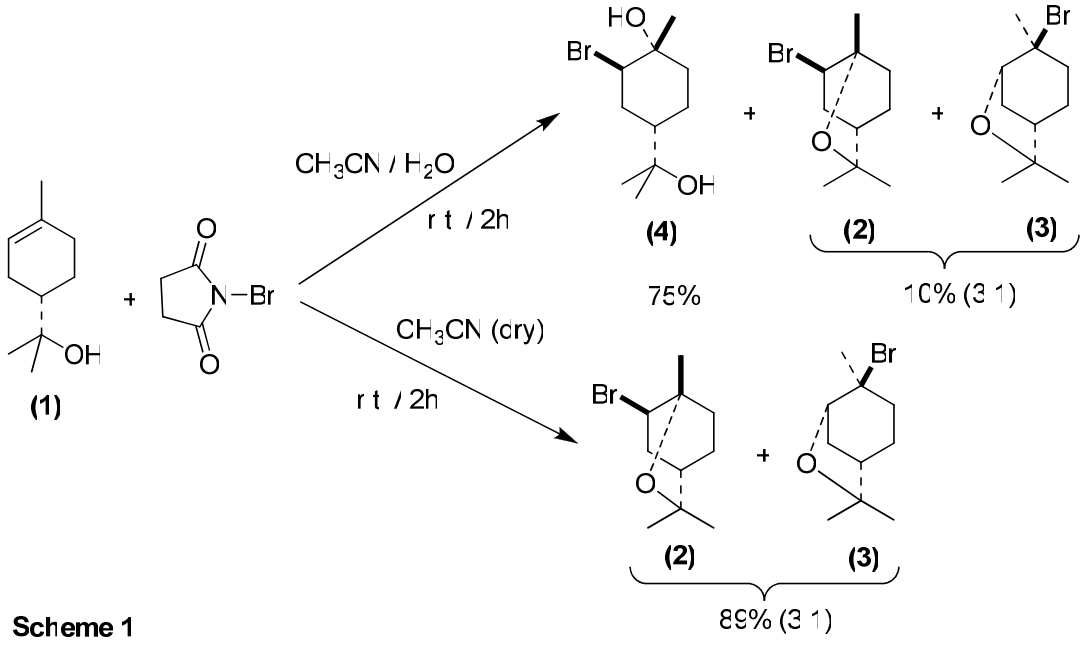


(NBS) **(1)** **(2)** **(3)**

Continuing our long interest on the chemical transformations involving natural abundant Brazilian monoterpenes,[9] we communicate here our results on the cohalogenation of (*S*)-α-terpineol with NBS in different solvents.

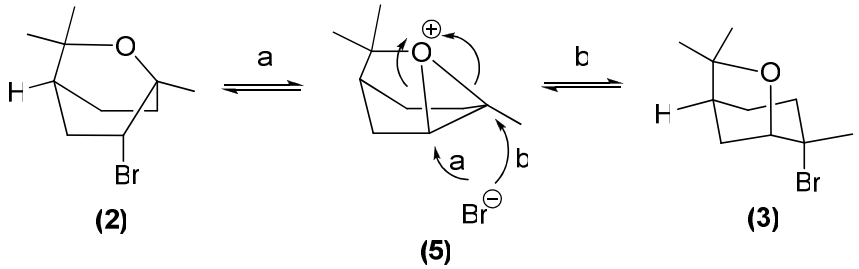
Results and Discussion

The reaction of (*S*)-α-terpineol (**1**) with equimolar NBS in aqueous acetonitrile at room temperature produced the bromohydrin (**4**) in 75% yield, along with 10% of a mixture of the bicyclic bromoethers (**2**) and (**3**) (3:1 by HRGC - high-resolution gas chromatography). On the other hand, the same reaction performed on dry acetonitrile produced the isomeric bicyclic bromoethers (**2**) and (**3**) as the unique products in 89% combined yield (once more 3:1, by HRGC) - Scheme 1. The products were identified by spectroscopic methods and the data for both bicyclic bromoethers are in good agreement with those previously reported.[8] Furthermore, chiral-HRGC analysis of bromohydrin (**4**) showed no significant loss of its optical purity (78%) when compared to starting α-terpineol (**1**) (76%).



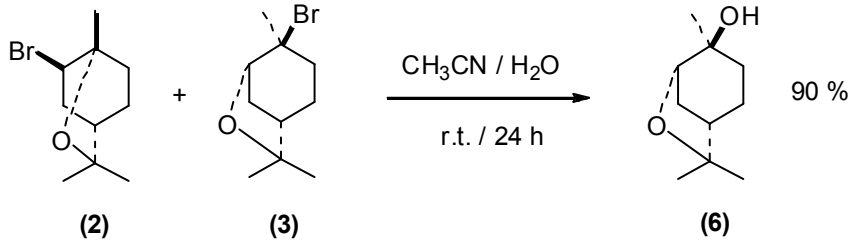
Scheme 1

Several attempts to separate the isomeric bicyclic bromoethers (**2**) and (**3**) showed unsuccessful as an interconversion occurs and consequently an equilibrium mixture of them was obtained in few minutes at room temperature.[6] This result could easily be explained through the oxonium ion (**5**)[8] shown in Scheme 2.



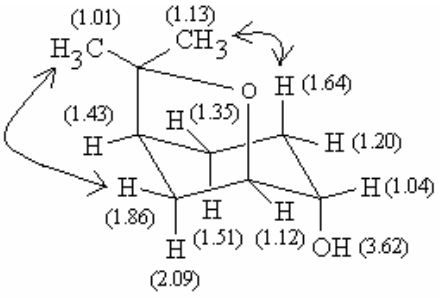
Scheme 2

Stirring the mixture of the bicyclic bromoethers (**2**) and (**3**) in aqueous acetonitrile led to 4-hydroxydihydropinol (**6**) in 90% isolated yield (Scheme 3). The chemical structure of (**6**) was unambiguously determined by ^{1}H and ^{13}C NMR 1D and 2D techniques.[10] Figure 1 shows its ^{1}H NMR chemical shifts and the observed correlations on the NOESY spectra.

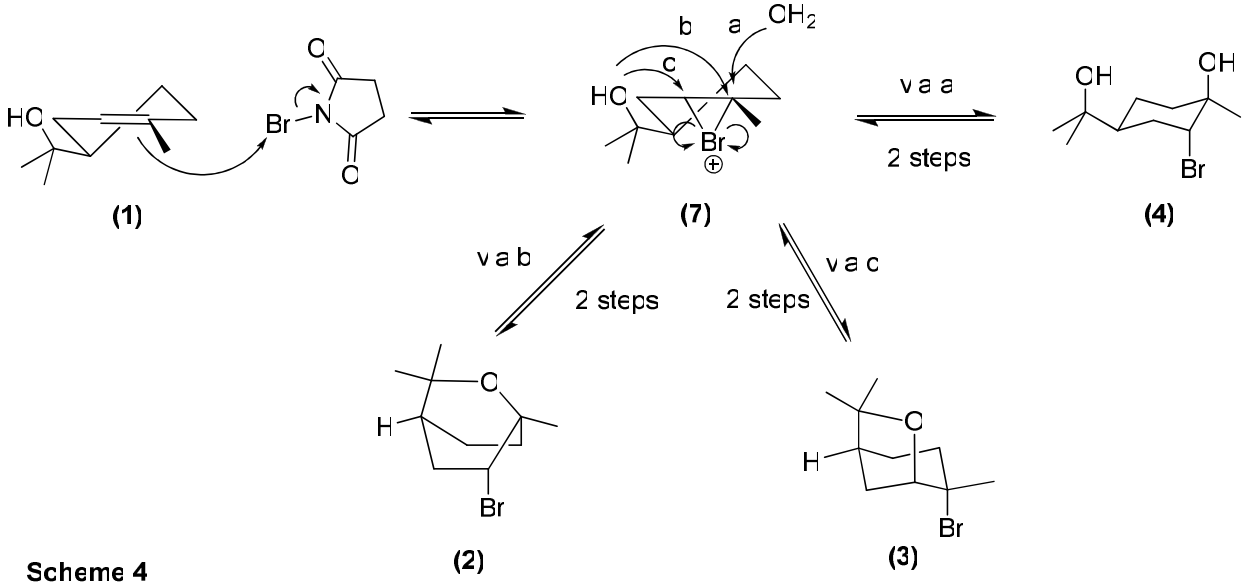


Scheme 3

Figure 1. ^{1}H NMR chemical shifts ($CDCl_3$, ppm) and NOESY correlations observed for 4-hydroxydihydropinol (**6**).

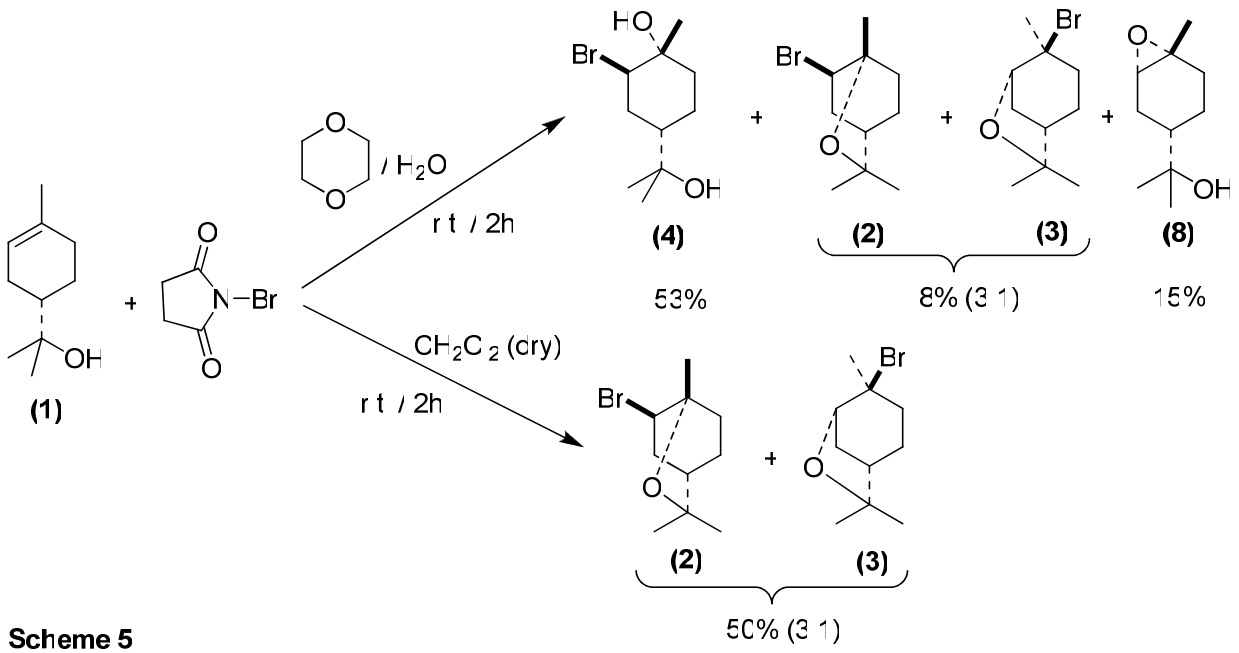


Based on the above results and assuming the most stable conformation of the bicyclic tetrahydrofuran ring being a bridged chair form,[11] a proposed rationalization is depicted in the Scheme 4. Initially an attack of the π system of α-terpineol to the electrophilic bromo atom of NBS occurs to produce a bromonium ion (**7**) *anti* to the bulk hydroxyisopropyl group, followed by its antiperiplanar opening by an axial nucleophilic attack[12] of water on the tertiary carbon to produce the *trans*-diaxial bromohydrin (**4**). However, a similar competitive intramolecular attack on the bromonium ion (**7**) by the hydroxyl group can occur leading to the bromotetrahydropyran (**2**), while the intramolecular attack on the secondary carbon led to the bromotetrahydrofuran (**3**). As expected, in the reaction performed in dry acetonitrile it is not possible to form the bromohydrin (**4**) and then the intramolecular reaction takes place to produce the bicyclic bromoethers.



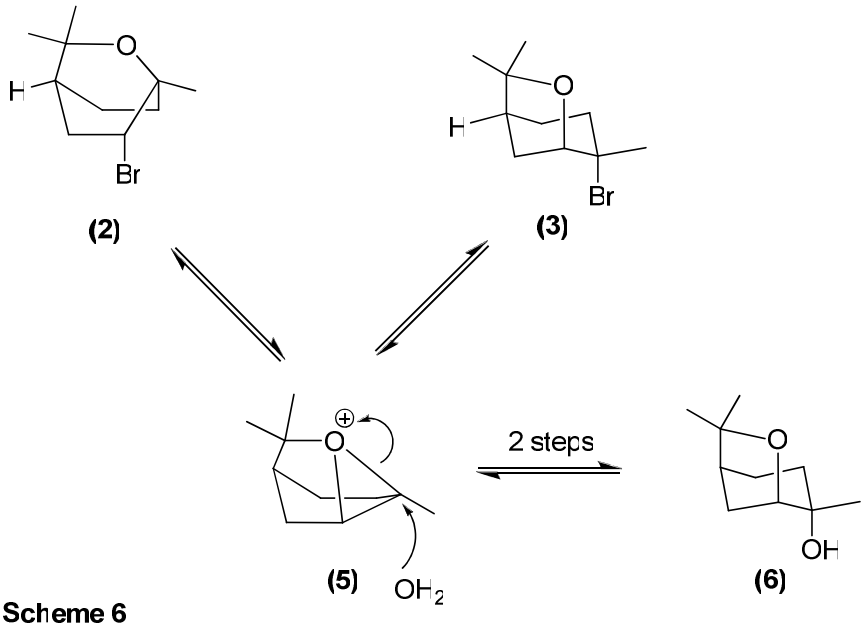
Scheme 4

In order to verify this hypothesis, the cohalogenation of α-terpineol was performed in dry dichloromethane and in aqueous THF. As expected, in dry CH_2Cl_2 it was produced the isomeric bicyclic bromoethers (**2**) and (**3**) (50% combined yield, 3:1 by HRGC) as the unique products, whilst in aqueous THF, along with the bromoethers (**2**) and (**3**) (8% combined yield, 3:1 by HRGC) and the bromoydrin (**4**) (53%), it was also obtained *cis*-α-terpineol oxide (**8**) in 15% (Scheme 5). The *cis* epoxide (**8**) is easily formed by cyclization of the bromohydrin (**4**) and was determined by mass spectrometry and by coinjection in HRGC with an authentic sample prepared by a known methodology.[13]



Scheme 5

The formation of 4-hydroxypinol (**6**) from the bicyclic bromoethers (**2**) and (**3**) could easily be understood by their solvolysis through the intermediacy of the oxonium ion (**5**), as depicted in Scheme 6.



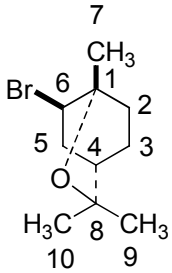
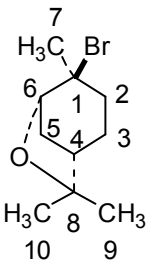
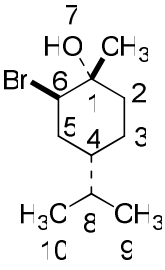
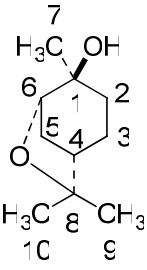
Scheme 6

Experimental Section

General

(*S*)-α-Terpineol was purchased from Dierberger (Brazil) and was distilled prior to use, $[\alpha]_D^{28}$ -76.0 (*c* 1.0, $CHCl_3$) - optical purity: 76% by both chiral-HRGC and polarimetry.[14] An authentic sample of *cis*-α-terpineol oxide (**8**) was prepared as described by Carman and Fletcher.[13] All other chemicals are commercially available and were used without further purification. Acetonitrile and dichloromethane were dried as described.[15] The ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometer for $CDCl_3$ solutions with TMS as internal standard. HRGC analysis were performed on a HP-5890-II gas chromatograph with FID by using a 30 m (length), 0.25 mm (ID) and 25 μm (phase thickness) RTX-5 silica capillary column and He (flow rate 50 cm/s) as carrier gas (split 1:20). Chiral-HRGC analyses were performed as early described.[16] Mass spectra were obtained on a Hewlett-Packard HP5896-A HRGC-MS using electron impact ionization (70 eV). Polarimetric analyses were performed on a Jasco DIP 370 polarimeter. Radial thin-layer chromatography was performed on a Harrison Research Chromatotron© (SiO_2, EtOAc/hexane 2:8 as eluent). Table 1 shows the ^{13}C NMR chemical shifts for all prepared compounds.

Table 1. ^{13}C chemical shifts ($CDCl_3$, ppm) for the isomeric bicyclic bromoethers (**2**), (**3**), bromohydrin (**4**), and 5-hydroxydidydropinol (**6**).

	 (**2**)	 (**3**)	 (**4**)	 (**6**)
C-1	74.4	68.9	72.9	70.5
C-2	52.5	83.2	33.0	81.5
C-3	37.0	35.0	21.9	30.7
C-4	34.7	41.8	41.8	40.3
C-5	21.8	24.4	31.7	23.3
C-6	25.4	37.0	60.2	30.0
C-7	26.1	34.7	30.3	27.5
C-8	73.1	83.6	72.3	80.8
C-9	28.8[a]	22.7	27.7[b]	22.2
C-10	28.0[a]	30.0	27.4[b]	29.1

[a, b] May be reversed.

*Cohalogenation of (*S*)-α-terpineol with NBS in aqueous acetonitrile.* (1*R*,2*R*,4*S*)-2-bromo-4-(2-hydroxypropan-2-yl)-1-methylcyclohexanol (**4**)

To a stirred solution of (*S*)-α-Terpineol (770 mg, 5 mmol) in acetonitrile/water (25 mL, 5:1), was added NBS (890 mg, 5 mmol) in small portions at room temperature. After 2 h, CH_2Cl_2 (25 mL) was added, the organic layer was separated, washed with 10% $CaCO_3$, 10% $Na_2S_2O_3$, brine and

then dried (Na_2SO_4). The solvent was evaporated to give a light reddish oil that was purified by thin-layer radial chromatography to give pure bromohydrin (**4**) (940 mg, 75%).
$[\alpha]_D^{28}$ - 41.2 (*c* 1.0, $CHCl_3$), optical purity: 78%, by chiral-HRGC.
^{1}H NMR δ ($CDCl_3$): 1.21 (s, 6H), 1.42 (s, 3H), 2.05 – 2.80 (m, 7H), 3.05 (s, 1H, OH), 3.08 (s, 1H, OH), 4.20 (1H, d) ppm.
The ^{13}C NMR chemical shifts are shown in Table 1.
MS: m/*z* 234 (M^++2 – H_2O), 232 (M^+ – H_2O), 219, 217, 176, 174, 153, 152, 95 (100%), 59, 43.

*Cohalogenation of (*S*)-α-terpineol with NBS in dry acetonitrile (or dry dichloromethane).* (1*R*,4*S*,5*S*)-4-bromo-4,7,7-trimethyl-6-oxabicyclo[3.2.1]octane (**2**) and (1*R*,4*S*,6*R*)-6-bromo-1,3,3-trimethyl-oxabicyclo[2.2.2]ocatane (**3**)
Same as above, using dry acetonitrile as solvent (30 mL). After work up, it was obtained 1.03 g (88% combined yield) of (**2**) and (**3**) (3:1, by HRGC).
Using dry dichloromethane as solvent, it was obtained 580 mg (50% combined yield) of (**2**) and (**3**) (3:1, by HRGC).
The ^{13}C NMR chemical shifts are shown in Table 1.
(**2**): MS: m/*z* 234 (M^++2), 232 (M^+), 217, 219, 153, 152, 97 (100%), 43.
(**3**): MS: m/*z* 234 (M^++2), 232 (M^+), 217, 219, 216, 214, 153, 152, 71, 43 (100%).

*Cohalogenation of (*S*)-α-terpineol with NBS in aqueous THF. Cis*-α-terpineol oxide (**8**).
Same as above, using THF/water as solvent (30 mL, 5:1). After work up, HRGC-MS indicated the isomeric bicyclic bromoethers (**2**) and (**3**) (8% combined yield, 3:1 by HRGC), the bromohydrin (**4**) (53%) and *cis*-α-terpineol oxide (**8**) (15%).
Analysis by coinjection in HRGC with an authentic sample[13] of *cis*-α-terpineol oxide indicated a unique peak.
(**8**): MS: m/*z* 155 (M^+ – CH_3), 152, 137, 126, 59, 43 (100%).

*Solvolysis of bromoethers (**2**) and (**3**).* (1*S*,2*S*,5*S*)-2,6,6-trimethyl-7-oxabicyclo[3.2.1]-octan-2-ol (**6**)
A mixture of (**2**) and (**3**) (233 mg, 1 mmol, 3:1 by HRGC) in acetonitrile/water (10 mL, 2/1) was stirred at room temperature for 48 h. Then, CH_2Cl_2 (25 mL) was added, the organic layer was separated and dried (Na_2SO_4). The solvent was evaporated giving a colorless residue that was purified by thin-layer radial chromatography to give pure 5-hydroxydihydropinol (**6**) (153 mg, 90%).
$[\alpha]_D^{28}$ + 25.6 (*c* 10.0, $CHCl_3$).
The ^{1}H and ^{13}C NMR chemical shifts are shown in Figure 1 and Table 1, respectively.
MS: m/*z* 170 (M^+), 126, 111, 109, 97, 83, 71, 43 (100%).

Conclusions
In summary, the cohalogenation of α-terpineol with NBS was revisited and our results showed that it is dependent on the solvent employed. Aqueous solvents (acetonitrile or THF) led mainly to the bromohydrin (**4**), while in dry solvents (acetonitrile or dichloromethane) there is an intramolecular reaction to produce the two bicyclic bromoethers (**2**) and (**3**).

Acknowledgements
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