

## Halomethoxylation of monoterpenes using (dichloriodo)benzene

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**Dedicated to Professor Nikolai Zefirov on his 70<sup>th</sup> birthday**

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### Abstract

Reactions of (dichloriodo)benzene or (dichloriodo)benzene/iodine with various monoterpenes in methanol provide a selective approach to the respective products of chloromethoxylation or iodomethoxylation of the double bond. The halomethoxylation of (+)-3-carene, carvone, and  $\beta$ -pinene proceeds with especially high regio- and stereoselectivity affording an appropriate single product in each case, while the reaction of limonene gives products of functionalization of both double bonds. This new methodology for the controlled introduction of halogen substituents into the structure of naturally occurring monoterpenes provides an entry into various potentially important synthetic intermediates.

**Keywords:** Monoterpenes, carene, carvone, pinene, limonene, (dichloriodo)benzene, chloromethoxylation, iodomethoxylation

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### Introduction

The controlled introduction of halogen substituents into the structure of naturally occurring monoterpenes provides an entry into a plethora of important synthetic intermediates and other practically useful products.<sup>1-4</sup> Numerous examples of bromination,<sup>2</sup> chlorination,<sup>3</sup> and iodination<sup>4</sup> of carvone, pinene, limonene, citral, camphen, pulegone and other terpenes and terpenoids have been reported in the literature. The most common and best investigated reaction is the bromination of terpenes using bromine,<sup>2a</sup> *N*-bromosuccinimide,<sup>2b</sup> and other brominating reagents.<sup>2c</sup> In contrast, the chemoselective introduction of chlorine or iodine into a terpene

structure represents a challenging problem. Several examples of a relatively selective chlorination of terpenoids with hypochlorous acid,<sup>3a</sup> *tert*-butylhypochlorite,<sup>3b</sup> or nitrosyl chloride<sup>3c</sup> were reported in the literature. Iodination of terpenes has previously been achieved by using iodine or *N*-iodosuccinimide.<sup>4</sup>

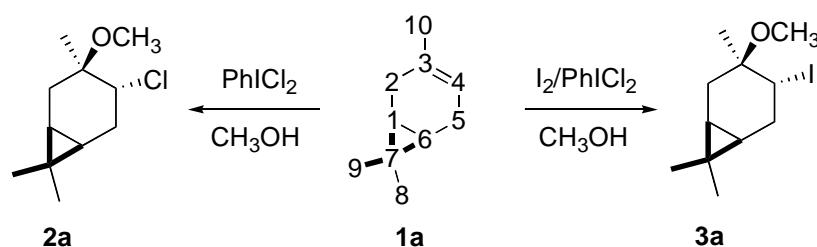
(Dichloroiodo)benzene is commonly used as an exceptionally selective chlorinating reagent.<sup>5</sup> In particular, it was demonstrated that (dichloroiodo)benzene can be used for the chlorination of the  $\alpha$ -santonin derivatives under free-radical conditions.<sup>6</sup> Recently, we reported that (dichloroiodo)benzene in methanol is a useful reagent for halomethoxylation of simple alkenes and alkynes.<sup>7</sup> Specifically, we have found that (dichloroiodo)benzene or a combination of (dichloroiodo)benzene with iodine can serve as an efficient source of the electrophilic "Cl<sup>+</sup>" or "I<sup>+</sup>" species, respectively, in the reactions with styrenes and arylacetylenes in the presence of methanol or water.<sup>7</sup> In the present work, we extend the reaction of halomethoxylation of unsaturated compounds to the more complex system of natural monoterpenes.

## Results and Discussion

We have investigated the reactions of (dichloroiodo)benzene or a combination (dichloroiodo)benzene/iodine in methanol with the following terpenes: (+)-3-carene (**1a**), carvone (**1b**),  $\alpha$ - and  $\beta$ -pinenes (**1c**), and limonene (**1d**). Yields of products and reaction conditions are shown in Table 1.

The reaction of (+)-3-carene (**1a**) with PhICl<sub>2</sub> in methanol at room temperature afforded product of *anti*-chloromethoxylation (**2a**) isolated by column chromatography in 42% yield. Under similar conditions, the reaction of carene (**1a**) with PhICl<sub>2</sub>/I<sub>2</sub> resulted in a selective formation of a single diastereomer (**3a**) isolated in 90% yield after column chromatography on silica gel (Scheme 1). The formation of single diastereomers (**2a**) and (**3a**) due to the Markovnikov-type *anti*-addition of the electrophilic reagent from the less sterically hindered side of the double bond in (**1a**) is in agreement with the typical reactivity of (+)-3-carene (for example, see bromoallenylxylation of (+)-3-carene<sup>8</sup>). The structure of products (**2a**) and (**3a**) was assigned based on high resolution NMR and HRMS. In particular, in <sup>1</sup>H NMR of the iodo-derivative **3a**, the vicinal coupling constants of H<sup>1</sup> atom (<sup>3</sup>J<sub>H1-H2</sub> = 10.1 and 4.4 Hz) and H<sup>6</sup> atom (<sup>3</sup>J<sub>H6-H5</sub> = 8.3 and 0.7 Hz) prove a half-chair conformation of the six-membered ring with atoms  $\beta$ H<sup>2</sup> and  $\alpha$ H<sup>5</sup> being *pseudo*-axial. Due to the *pseudo*-axial position, atom  $\beta$ H<sup>2</sup> is shielded by the cyclopropane ring (up-field shift by 0.7 ppm as compared to  $\alpha$ H<sup>2</sup>). Atom H<sup>4</sup> in the iodo-derivative occupies an axial position (<sup>3</sup>J<sub>H4-H5</sub> = 11.6 and 6.9 Hz) indicating  $\alpha$ -orientation of the iodine atom. Long-range spin-spin coupling <sup>4</sup>J<sub>3H10- $\beta$ H2</sub> = 0.7 Hz is possible only in the case of the axial methyl *trans* to  $\beta$ H<sup>2</sup>, so the methoxy group is  $\beta$ -oriented. The configuration found (3- $\beta$ -methoxy, 4- $\alpha$ -iodo-) is in agreement with the typical asynchronous electrophilic *trans*-addition to 3-carene: primary attack of the electrophile (I<sup>+</sup>) from the less hindered  $\alpha$ -side of the C=C bond of

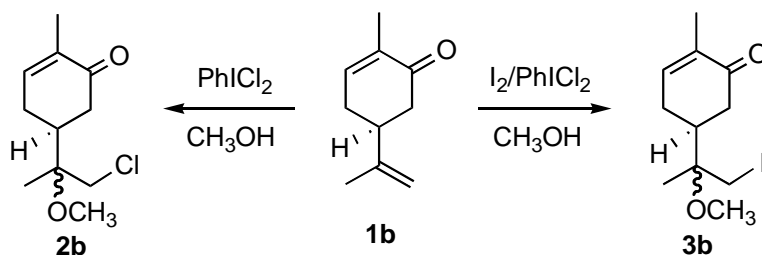
the planar six-membered cycle<sup>9</sup> followed by addition of nucleophilic particle (CH<sub>3</sub>OH) from the opposite side.



### Scheme 1

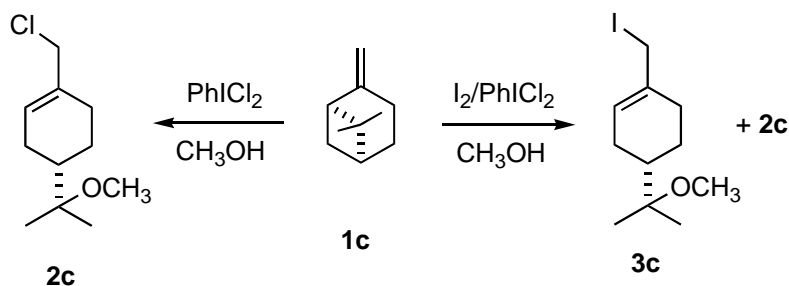
In contrast to (+)-3-carene, the reaction of 2-carene with PhICl<sub>2</sub>/I<sub>2</sub> resulted in the formation of a complex mixture of unstable products.

The reaction of carvone (1b) with PhICl<sub>2</sub> or PhICl<sub>2</sub>/I<sub>2</sub> in methanol selectively afforded the respective products of chloromethoxylation (2b) or iodomethoxylation (3b) of the terminal double bond, which were isolated by column chromatography in good yields (Scheme 2). It is interesting to note that the previously reported chlorination of (+)-carvone with hypochlorous acid<sup>10a</sup> or the electrochemical chlorination<sup>10b</sup> of carvone led to a selective formation of the allylic chloride, 9-chlorocarvone. It was also reported that the bromination of carvone resulted in a nonselective addition to both double bonds and carbon C-6 affording the respective tetra- and pentabromide adducts.<sup>11</sup>

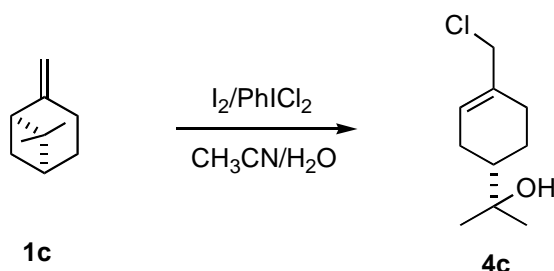


### Scheme 2

The reaction of  $\alpha$ -pinene and  $\alpha$ -terpineol with PhICl<sub>2</sub> in methanol resulted only in the formation of a black tar, while a similar reaction of  $\beta$ -pinene (1c) afforded the product of ring opening (2c) (Scheme 3). Under conditions of iodomethoxylation, the reaction of  $\beta$ -pinene (1c) PhICl<sub>2</sub>/I<sub>2</sub> in methanol afforded a 3:2 mixture of the expected iodide (3c) and the chloride (2c). Likewise, only the chloride (4c), instead of the expected iodide, was isolated from the reaction of  $\beta$ -pinene with PhICl<sub>2</sub>/I<sub>2</sub> in aqueous acetonitrile (Scheme 4).



Scheme 3

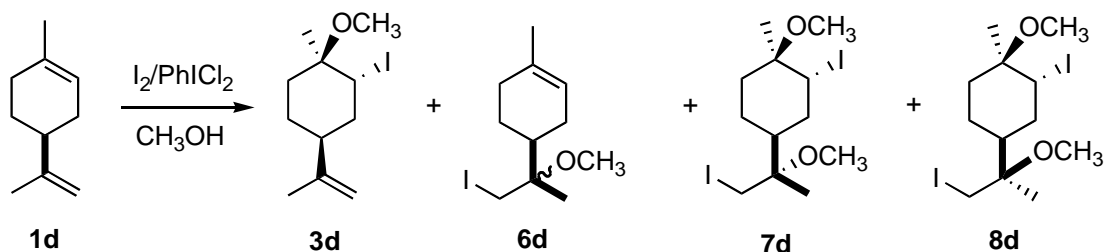


Scheme 4

A similar formation of the products of ring opening in the reaction of  $\beta$ -pinene with iodine<sup>11a</sup> and  $\text{NaOCl}/\text{CeCl}_3$ <sup>11b</sup> was previously reported in the literature. At the same time, the reaction of  $\beta$ -pinene with *N*-chlorosuccinimide in the presence of catalytic diphenyldiselenide (3%) leads to the products of allylic chlorination with preserved pinene skeleton.<sup>11c</sup>

Only few examples of halogenation reactions of limonene (**1d**) were previously reported.<sup>13</sup> In particular, it was found that bromine adds to both double bonds of limonene with the formation of the respective tetrabromide,<sup>13a</sup> while the reaction of limonene with *tert*-butyl hypochlorite leads to a complex mixture of mono- and dichlorides due to the allylic chlorination or electrophilic addition to the internal double bond.<sup>13b</sup>

We have found that the chloromethoxylation reaction of limonene with  $\text{PhICl}_2$  in methanol has a low selectivity and leads to a large number of products, which we were not able to isolate and identify. The iodomethoxylation of limonene with  $\text{PhICl}_2/\text{I}_2$  in methanol was more selective and we were able to isolate two major chromatographic fractions from the reaction mixture: the first fraction containing regioisomers **3d** and **6d** and the second fraction – diastereomers **7d** and **8d** (Scheme 5).



### Scheme 5

It should be emphasized that the reactions of iodomethoxylation in all cases were more selective compared to the chloromethoxylation. In particular, the GC-MS analysis of the reaction mixtures resulting from the chloromethoxylation of terpenes **1a-1c** indicated the presence of polychlorinated compounds as by-products in these reactions. The formation of these polychlorinated by-products explains relatively lower preparative yields of the products of chloromethoxylation (see Table 1).

**Table 1.** Halomethoxylation of monoterpenes **1a-d** using (dichloroiodo)benzene via Schemes 1-5

Entry	Monoterpene	Product	Conditions <sup>a</sup>	Time (min)	Yield <sup>b</sup> %
1	<b>1a</b>	<b>2a</b>	PhICl <sub>2</sub> , CH <sub>3</sub> OH	20	42
2	<b>1a</b>	<b>3a</b>	I <sub>2</sub> , PhICl <sub>2</sub> , CH <sub>3</sub> OH	15	90
3	<b>1b</b>	<b>2b</b>	PhICl <sub>2</sub> , CH <sub>3</sub> OH	20	43
4	<b>1b</b>	<b>3b</b>	I <sub>2</sub> , PhICl <sub>2</sub> , CH <sub>3</sub> OH	15	62
5	<b>1c</b>	<b>2c</b>	PhICl <sub>2</sub> , CH <sub>3</sub> OH	20	35
6	<b>1c</b>	<b>2c</b>	I <sub>2</sub> , PhICl <sub>2</sub> , CH <sub>3</sub> OH	15	35
		<b>3c</b>			23
7	<b>1c</b>	<b>4c</b>	I <sub>2</sub> , PhICl <sub>2</sub> , CH <sub>3</sub> CN, H <sub>2</sub> O	15	21
8	<b>1d</b>	<b>3d+6d</b>	I <sub>2</sub> , PhICl <sub>2</sub> , CH <sub>3</sub> OH	15	22
		<b>7d+8d</b>			13

<sup>a</sup> All reactions were conducted at room temperature.

<sup>b</sup> Preparative yields of products isolated after column chromatography.

In conclusion, the reactions of (dichloroiodo)benzene or (dichloroiodo)benzene/iodine with various monoterpenes in methanol provide a generally selective approach to the respective products of chloromethoxylation or iodomethoxylation of the double bond. The halomethoxylation of 3-carene, carvone, and  $\beta$ -pinene proceeds with especially high regio- and stereoselectivity affording an appropriate single product in each case, while the reaction of limonene gives products of functionalization of both double bonds. This new methodology for

the controlled introduction of halogen substituents into the structure of naturally occurring monoterpenes provides an entry into various potentially important synthetic intermediates.

## Experimental Section

**General Procedures.** IR spectra were recorded on a Bruker Vector-22 spectrophotometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AC-200 NMR spectrometer (200 and 50 MHz), AM-400 (400 and 100 MHz) and DRX 500 (500 and 125 MHz) using  $\text{Me}_4\text{Si}$  as internal standard and  $\text{CDCl}_3$  or  $\text{CDCl}_3\text{-CCl}_4$  1:3. Chemical shifts are reported in parts per million (ppm). GC-MS spectra were obtained using Hewlett Packard 5890/II gas chromatograph equipped with quadrupole mass-spectrometer as detector (HP MSD 5971). High resolution EI mass spectra (EI, 70 eV) were recorded on Finnigan MAT 8200 mass spectrometer. Flash column chromatography was performed on silica gel L40/100  $\mu\text{m}$  from Chemapol. Thin layer chromatography was carried out using TLC plates Sorbfil with fixed  $\text{SiO}_2$  layer. TLC plates were developed by spraying with the ethanol solution of vanillin (2 g vanillin and 5 ml concentrated  $\text{H}_2\text{SO}_4$  in 150 ml EtOH) or  $\text{FeCl}_3$  (10% solution of  $\text{FeCl}_3$  in EtOH) followed by heating. All solvents were distilled before use. Pinenes were purchased from Fluka; limonene, carene and carvone were purchased from Aldrich. (Dichloroiodo)benzene was prepared by chlorination of iodobenzene with chlorine gas.

### General procedure for chloromethoxylation of monoterpenes 1a-d with (dichloroiodo)-benzene in methanol

(Dichloroiodo)benzene (0.281 g, 1.02 mmol) was added to a solution of monoterpene (1.0 mmol) in  $\text{CH}_3\text{OH}$  (3.0 ml) and the mixture was stirred for 20 min at room temperature. The resulting mixture was poured into water (30 ml), extracted by ether (2x30 ml), washed with 5%- $\text{NaHCO}_3$  (15 ml), water (2x50 ml), and saturated solution of  $\text{NaCl}$  (50 ml), and dried with  $\text{Na}_2\text{SO}_4$ . Ether was evaporated and the residue was dissolved in hexane (3 ml) and separated by column chromatography using hexane first to isolate iodobenzene and then 5:1 mixture hexane-benzene to isolate reaction products **2a**, **2b**, and **2c**.

### General procedure for iodomethoxylation of monoterpenes 1a-d with (dichloroiodo)benzene/iodine in methanol

(Dichloroiodo)benzene (0.275 g, 1.0 mmol) was added to a solution of iodine (0.267 g, 1.05 mmol) in  $\text{CH}_3\text{OH}$  (7.0 ml) and the mixture was stirred for 5 min at room temperature. The resulting mixture was added to a solution of monoterpene (2.0 mmol) in  $\text{CH}_3\text{OH}$  (1.0 ml) and the mixture was stirred for 10 min at room temperature. The resulting mixture was poured into 5% aq.  $\text{Na}_2\text{S}_2\text{O}_3$  (20 ml) and treated as described in the previous procedure. Column chromatography using hexane first and then 5:1 mixture hexane-benzene afforded products **3a**, **3b**, **3c**, **3d**, **6d**, **7d** and **8d**.

**Compound characterization**

**(1S,3R,4R,6R)-4-Chloro-3-methoxy-3,7,7-trimethylbicyclo[4.1.0]heptane (2a).** oil; IR,  $\nu_{\max}$ , (neat,  $\text{cm}^{-1}$ ): 1115 (C-O-CH<sub>3</sub>), 657 (C-Cl); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.67 (1H, ddd, H-6,  $J_1 = 9.9$ ,  $J_2 = 8.3$ ,  $J_3 = 0.7$  Hz), 0.71 (1H, ddd, H-1,  $J_1 = 10.1$ ,  $J_2 = 9.9$ ,  $J_3 = 4.4$  Hz), 1.00 and 1.02 (3H, s, H-8 and/or 3H, s, H-9), 1.27 (3H, d, H-10,  $J = 0.7$  Hz), 1.48 (1H, ddq, H-2 $\beta$ ,  $J_1 = 14.2$ ,  $J_2 = 4.4$ ,  $J_3 = 0.7$  Hz), 2.00 (1H, dd, H-2 $\alpha$ ,  $J_1 = 14.2$ ,  $J_2 = 10.1$  Hz); 2.10 (1H, ddd, H-5 $\beta$ ,  $J_1 = 15.0$ ,  $J_2 = 6.9$ ,  $J_3 = 0.7$  Hz); 2.25 (1H, ddd, H-5 $\alpha$ ,  $J_1 = 15.0$ ,  $J_2 = 11.6$ ,  $J_3 = 8.3$  Hz), 3.22 (3H, s, OCH<sub>3</sub>), 3.82 (1H, dd, H-4,  $J_1 = 11.6$ ,  $J_2 = 6.9$  Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  15.53 (C-8), 16.61 (C-1), 17.75 (C-7), 19.42 (C-6), 20.73 (C-10), 28.59 (C-9), 29.16 (C-5), 30.41 (C-2), 48.73 (OCH<sub>3</sub>), 64.13 (C-4), 75.44 (C-3); HRMS: calcd for C<sub>11</sub>H<sub>19</sub>ClO (M<sup>+</sup>): 202.11243, found m/z 202.11158; MS (EI, 70 eV) m/z (%): 202/204 (M<sup>+</sup>, 3), 187/189 (6), 170/172 (12), 149 (38), 135 (100), 119 (22), 106 (53), 93 (59), 85 (39), 73 (25), 55 (21), 43 (30).

**(1S,3R,4R,6R)-4-Iodo-3-methoxy-3,7,7-trimethylbicyclo[4.1.0]heptane (3a).** oil; IR,  $\nu_{\max}$ , (neat,  $\text{cm}^{-1}$ ): 1107 (C-O-CH<sub>3</sub>), 599 (C-I); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  0.45 (1H, ddd, H-6,  $J_1 = 9.9$ ,  $J_2 = 8.3$ ,  $J_3 = 0.7$  Hz), 0.71 (1H, ddd, H-1,  $J_1 = 10.1$ ,  $J_2 = 9.9$ ,  $J_3 = 4.4$  Hz), 0.86 and 0.93 (3H, s, H-8 and/or 3H, s, H-9), 1.19 (3H, d, H-10,  $J = 0.7$  Hz); 1.31 (1H, ddq, H-2 $\beta$ ,  $J_1 = 14.2$ ,  $J_2 = 4.4$ ,  $J_3 = 0.7$  Hz), 2.01 (1H, dd, H-2 $\alpha$ ,  $J_1 = 14.2$ ,  $J_2 = 10.1$  Hz); 2.37 (1H, ddd, H-5 $\beta$ ,  $J_1 = 15.0$ ,  $J_2 = 6.9$ ,  $J_3 = 0.7$  Hz), 2.54 (1H, H-5 $\alpha$ ,  $J_1 = 15.0$ ,  $J_2 = 11.6$ ,  $J_3 = 8.3$  Hz), 3.06 (3H, s, OCH<sub>3</sub>); 3.98 (1H, dd, H-4,  $J_1 = 11.6$ ,  $J_2 = 6.9$  Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  15.10 (C-8), 17.45 (C-7), 19.56 and 19.62 (C-1 and/or C-6), 21.98 (C-10), 26.90 (C-5), 28.43 (C-9), 33.86 (C-2), 41.08 (C-4), 48.28 (OCH<sub>3</sub>), 73.88 (C-3); HRMS: calcd for C<sub>11</sub>H<sub>18</sub>O (M-HI)<sup>+</sup>: 166.13576, found m/z 166.13244; MS (EI, 70 eV) m/z (%): 294 (M<sup>+</sup>, <1), 167 (6), 166 (19), 151 (22), 142 (41), 135 (26), 106 (53), 119 (44), 93 (100), 85 (39), 67 (33), 59 (23), 55 (24), 43 (68).

**5-(1-Chloro-2-methoxypropan-2-yl)-2-methylcyclohex-2-enone (2b), mixture of epimers (2:1).** oil; IR,  $\nu_{\max}$ , (neat),  $\text{cm}^{-1}$ : 1724 (C=C), 1675 (C=O), 1257 (CH<sub>2</sub>-Cl), 1039 (C-O-CH<sub>3</sub>), 751 (C-Cl); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.12 (3H, s, H-9); 1.70 (3H, s, H-10); 2.05-2.5 (5H, m, H-4, H-5, H-6); 3.18 (3H, s, OCH<sub>3</sub>); 3.29-3.46 (2H, m, H-8); 6.63 (0.65H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz), 6.67 (0.35H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  (main isomer) 15.79 (C-10), 18.07 (C-9), 27.20 (C-4), 38.64 (C-6), 41.10 (C-5), 47.89 (C-8), 49.97 (OCH<sub>3</sub>), 77.22 (C-7), 136.02 (C-2), 143.18 (C-3), 198.34 (C-1); (minor isomer) 15.79 (C-10), 17.99 (C-9), 26.46 (C-4), 39.24 (C-6), 41.10 (C-5), 47.25 (C-8), 50.09 (OCH<sub>3</sub>); 77.86 (C-7), 135.74 (C-2), 144.03 (C-3), 198.34 (C-1); HRMS: calcd for C<sub>11</sub>H<sub>17</sub>ClO<sub>2</sub> (M<sup>+</sup>): 216.09170, found m/z 216.09215; MS (EI, 70 eV) m/z (%): 216/218 (M<sup>+</sup>, <1), 184/186 (3), 167 (15), 149 (2), 135 (17), 121 (4), 110 (56), 109 (66), 108 (34), 107 (100), 95 (11), 93 (9), 82 (9), 79 (13), 73 (29), 57 (42), 53 (10), 43 (10), 41 (14).

**5-(1-Iodo-2-methoxypropan-2-yl)-2-methylcyclohex-2-enone (3b), mixture of epimers (5:4).** oil; IR,  $\nu_{\max}$ , (neat),  $\text{cm}^{-1}$ : 1720 (C=C), 1672 (C=O), 1076 (C-O-CH<sub>3</sub>), 614 (C-I); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  (main isomer) 1.25 (3H, s, H-9), 1.73 (3H, s, H-10), 2.12-2.50 (5H, m, H-4, H-5, H-6), 3.18 (3H, s, OCH<sub>3</sub>), 3.21-3.29 (2H, s, H-8), 6.68 (1H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz, H-2);  $\delta$  (minor isomer) 1.26 (3H, s, H-9), 1.73 (3H, s, H-10), 2.12-2.50 (5H, m, H-4, H-5, H-6), 3.17 (3H, s, OCH<sub>3</sub>), 3.21-3.29 (2H, m, H-8), 6.63 (1H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz, H-2); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$

(main isomer) 12.22 (C-8), 15.82 (C-10), 18.82 (C-9), 26.25 (C-4), 39.08 (C-6), 41.92 (C-5), 49.31 (OCH<sub>3</sub>), 75.17 (C-7), 135.42 (C-2), 142.99 (C-3), 198.16 (C-1);  $\delta$  (minor isomer) 12.32 (C-8), 15.82 (C-10), 18.95 (C-9), 27.02 (C-4), 38.43 (C-6), 42.05 (C-5), 49.47 (OCH<sub>3</sub>); 74.97 (C-7), 135.78 (C-2), 144.11 (C-3), 198.36 (C-1); HRMS: calcd for C<sub>11</sub>H<sub>17</sub>IO<sub>2</sub> (M<sup>+</sup>): 308.02751, found m/z 308.02889; MS (EI, 70 eV) m/z (%): 308 (M<sup>+</sup>, <1), 199 (86), 167 (9), 149 (14), 121 (8), 109 (21), 107 (36), 93 (10), 91 (10), 82 (11), 81 (17), 73 (43), 72 (100), 59 (12), 55 (12), 43 (20), 41 (33).

**1-(Chloromethyl)-4-(2-methoxypropan-2-yl)cyclohex-1-ene (2c).** oil; IR,  $\nu_{\max}$ , (neat), cm<sup>-1</sup>: 1259 (CH<sub>2</sub>-Cl), 1079 (C-O-CH<sub>3</sub>), 682 (C-Cl); <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  1.08 and 1.09 (3H, s, H-9 and/or 3H, s, H-10), 1.20 – 2.15 (7H, m, H-3, H-4, H-5, H-6), 3.14 (3H, s, OCH<sub>3</sub>), 3.94 (2H, s, H-7), 5.77 (1H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz, H-2); <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  21.98 and 22.21 (C-9 and/or C-10), 23.50 (C-5), 26.81 and 27.04 (C-3 and/or C-6), 41.86 (C-4), 48.68 (OCH<sub>3</sub>), 49.66 (C-7), 76.11 (C-8), 127.16 (C-2), 134.45 (C-1); HRMS: calcd for C<sub>11</sub>H<sub>19</sub>ClO (M<sup>+</sup>): 202.11243, found m/z 202.11239; MS (EI, 70 eV) m/z (%): 202/204 (M<sup>+</sup>, 1), 170/172 (4), 166 (7), 135 (10), 134 (30), 123 (11), 119 (24), 105 (11), 93 (19), 91 (25), 84 (15), 73 (100), 55 (12), 43 (13).

**2-(4-(Chloromethyl)cyclohex-3-enyl)propan-2-ol (4c).** IR,  $\nu_{\max}$ , (neat), cm<sup>-1</sup>: 3354 (OH), 1274 (CH<sub>2</sub>-Cl), 1086 (C-OH), 682 (C-Cl); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> – CCl<sub>4</sub> – 1:3)  $\delta$  1.10 and 1.12 (3H, s, H-9 and/or 3H, s, H-10), 1.22 – 2.22 (7H, m, H-3, H-4, H-5, H-6), 3.90 (2H, s, H-7), 5.72 (1H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz, H-2); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>/CCl<sub>4</sub> – 1:3)  $\delta$  23.46 (C-5), 25.59 and 27.45 (C-9 and/or C-10), 26.79 and 26.86 (C-3 and/or C-6), 44.60 (C-4), 49.48 (C-7), 72.13 (C-8), 126.77 (C-2), 134.30 (C-1); HRMS: calcd for C<sub>11</sub>H<sub>19</sub>ClO (M<sup>+</sup>): 188.09679, found m/z 188.09653; MS (EI, 70 eV) m/z (%): 188/190 (M<sup>+</sup>, <1), 187/189 (<1), 170/172 (14), 161/163 (11), 153 (100), 147/149 (10), 135 (15), 121 (19), 119 (21), 107 (23), 96 (50), 91 (23), 81 (91), 73 (32), 55 (19), 41 (23).

**1-(Iodomethyl)-4-(2-methoxypropan-2-yl)cyclohex-1-ene (3c).** oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.01 and 1.03 (3H, s, H-9 and/or 3H, s, H-10), 1.18 – 2.18 (7H, m, H-3, H-4, H-5, H-6), 3.10 (3H, s, OCH<sub>3</sub>), 3.81 (2H, s, H-7), 5.89 (1H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz, H-2); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  12.88 (C-7), 21.86 and 22.07 (C-9 and/or C-10), 23.43 (C-5), 26.92 and 28.17 (C-3 and/or C-6), 41.75 (C-4), 48.55 (OCH<sub>3</sub>), 49.66 (C-7), 75.88 (C-8), 126.19 (C-2), 135.35 (C-1).

**(1R,2R,4S)-2-Iodo-1-methoxy-1-methyl-4-(prop-1-en-2-yl)cyclohexane (3d).** oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.16 (3H, s, H-10), 1.62 (3H, s, H-9), 1.20 – 2.54 (7H, m, H-3, H-4, H-5, H-6), 3.15 (3H, s, OCH<sub>3</sub>); 4.55 (2H, s, H-2), 4.54 (1H, ddd, H-8, J=2.8, 2.8, 2.8 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  17.91 (C-9), 23.42 (C-5), 23.52 (C-10), 33.63 and 36.97 (C-3, and/or C-6), 39.81 (C-4), 40.08 (C-2), 48.80 (OCH<sub>3</sub>), 75.84 (C-1), 109.50 (C-8), 148.43 (C-7); HRMS: calcd for C<sub>11</sub>H<sub>19</sub>IO (M<sup>+</sup>): 294.04810, found m/z 294.04824.

**4-(1-Iodo-2-methoxypropan-2-yl)-1-methylcyclohex-1-ene (6d), mixture of two isomers (1:1).** oil; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  (first isomer) 1.35 (3H, s, H-9), 1.62 (3H, s, H-10), 1.20 – 2.54 (7H, m, H-3, H-4, H-5, H-6), 3.17 (3H, s, OCH<sub>3</sub>); 3.22-3.36 (2H, m, H-8), 5.30 (1H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz, H-2);  $\delta$  (second isomer) 1.36 (3H, s, H-9), 1.70 (3H, s, H-10), 2.20 – 2.54 (7H, m, H-3, H-4, H-5, H-6), 3.18 (3H, s, OCH<sub>3</sub>); 3.22-3.36 (2H, m, H-8), 5.35 (1H, m<sub>1</sub> W<sub>1/2</sub>=10 Hz, H-



2);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  (first isomer) 14.63 (C-8), 21.32 and 25.99 (C-9 and/or C-10), 24.25 (C-5), 26.64 and 30.99 (C-3 and/or C-6), 48.95 ( $\text{OCH}_3$ ), 75.74 (C-7), 120.05 (C-2), 134.25 (C-1);  $\delta$  (second isomer) 14.99 (C-8), 21.32 and 25.99 (C-9 and/or C-10), 25.73 (C-5), 26.31 and 30.86 (C-3 and/or C-6), 49.24 ( $\text{OCH}_3$ ); 75.84 (C-7), 120.97 (C-2), 134.26 (C-1); HRMS: calcd for  $\text{C}_{11}\text{H}_{19}\text{IO}$  ( $\text{M}^+$ ): 294.04810, found  $m/z$  294.04824.

**2-Iodo-4-(2-iodo-1-methoxy-1-methyl-ethyl)-1-methoxy-1-methyl-cyclohexane (7d and 8d, mixture (1:1)).** oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  (first isomer) 1.12 (3H, s, H-9), 1.29 (3H, s, H-10), 2.18-2.24 (2H, m, H-3), 1.39-1.48 (2H, m, H-5), 1.62-1.70 (2H, m, H-6), 1.82-1.92 (1H, m, H-4), 3.12 (3H, s,  $\text{OCH}_3$ ), 4.52 (1H, ddd  $J=2.8, 2.8, 2.8$  Hz, H-2);  $\delta$  (second isomer) 1.18 (3H, s, H-9), 1.35 (3H, s, H-10), 2.18-2.24 (2H, m, H-3), 1.39-1.48 (2H, m, H-5), 1.62-1.70 (2H, m, H-6), 1.82-1.92 (1H, m, H-4), 3.13 (3H, s,  $\text{OCH}_3$ ), 4.55 (1H, ddd  $J=2.8, 2.8, 2.8$  Hz, H-2);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  (first isomer) 14.89 (C-8), 20.40 (C-10), 21.54 (C-5), 25.79 (C-9), 30.89 (C-5), 32.44 (C-6), 37.94 (C-2), 39.79 (C-4), 48.66 and 48.81 ( $\text{OCH}_3$ ), 74.26 (C-1), 75.27 (C-7);  $\delta$  (second isomer) 15.16 (C-8), 20.57 (C-10), 22.11 (C-5), 25.79 (C-9), 31.23 (C-5), 32.67 (C-6), 38.44 (C-2), 39.96 (C-4), 49.12 and 49.19 ( $\text{OCH}_3$ ), 74.35 (C-1), 75.35 (C-7).

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