Effect of bridgehead substitution in the Grob fragmentation of norbornyl ketones: a new route to substituted halophenols‡

Sumit Choudhury, a Saeed Ahmad a and Faiz Ahmed Khan b

Grob fragmentation of suitably designed bicyclic species often generates novel organic skeletons in a facile manner. Herein, we report a comprehensive account of an effective acid-catalyzed Grob fragmentation of trihalonorbornyl ketones to dihalophenol derivatives in good yields. The transformation entails tri-n-butyltin hydride (TBTH) mediated regioselective reduction of one of the two bridgehead halogens of readily available Diels–Alder adducts resulting from 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadiene and vinyl acetate derivatives, followed by its conversion to substituted halophenol species via a three-step hydrolysis–oxidation–rearrangement/aromatization strategy. Both alkyl and aryl substituted norbornyl ketones were studied. A detailed mechanistic analysis employing an isotope labeling experiment revealed plausible mechanistic pathways. Among the two bridgehead substituents, when halogen (X = Cl, Br) stays at C-1 and hydrogen (H, or deuterium, D) at C-4, then product formation takes place via exclusive protonation (supplied by an external acid) at β carbon (i.e. C-1) of a dienol moiety formed in situ during the Grob-fragmentation, followed by the removal of acidic 4-H (or 4-D) and halide ion (X−) from the resulting cyclohexenone intermediate prior to nucleophilic attack on the oxocarbenium ion by X− and final enolisation of cyclohexadienone species. A sharp deviation was observed with the regioisomeric bicyclic ketone, wherein the 4-X triggers a facile removal of X− and forms the end products without necessitating the involvement of the C-1 substituent (i.e. 1-H/D), thereby retaining it in the final halophenols. It clearly demonstrates how the bridgehead substituents in the two regioisomeric trihalo-norbornyl ketones steer the bicyclic systems to follow entirely different reaction pathways thus suggesting their crucial yet distinct roles in the overall reaction. The present transformation thus manifests the relevance of bridgehead substituents in the Grob fragmentation of such norbornyl systems. Our current strategy also allows one to access ortho-deuterated halophenol compounds.

Introduction

Since the pioneering report in the mid-20th century, Grob fragmentation, which is a heterolytic sigma bond cleavage of a carbon–heteroatom-based five-atom aliphatic chain containing an electrofuge and a nucleofuge at positions 1 and 3, respectively, has emerged as a potential tool to achieve highly rewarding organic transformations. In particular, its utilization on a rigid bicyclic template is particularly appealing as manifested in the synthesis of complex organic skeletons as well as bioactive natural products. In consequence of our continued interests in the exploration of the Grob fragmentation strategy over suitably fashioned norbornyl species in generating novel organic skeletons, earlier we described the synthesis of halophenol derivatives, and from the acid-catalysed fragmentation of tetrahalo- and dihalo-bicyclic ketones and, respectively (eqn (1) and (2), Scheme 1). Both compounds 1 and 3 (eqn (1) and (2), Scheme 1), which differ from each other in the substitution pattern at the bridgehead positions, undergo initial acid-mediated fragmentation in an identical fashion via the Grob strategy involving C1–C7 sigma bond cleavage, but they differed in the later stages depending upon the substitution pattern at the bridgeheads thus giving rise to different end products. This strategy was further employed on norbornyl α-diketones eventually affording substituted aromatic compounds via the intermediate formation of α-ketoenols and since there is no example in the literature on regiospecific utilization of two bridgehead...
positions of tetrahalo norbornyl species 1, as a further extension to our previous work, we envisioned that judicious exploitation of the difference in the chemical environment surrounding the two bridgehead halogens would enable us to regioselectively replace each one of them leading to two regioisomeric trihalo ketones 9 and 10 (eqn (4), Scheme 1) which might be interesting candidates for the investigation of a similar acid-mediated Grob fragmentation. Of additional interest is to distinguish the precise impact of the two bridgehead substituents during the mechanistic course of trihalo-norbornyl ketone fragmentation. Herein we present a synthetic sequence for the formation of regioisomeric trihalo-norbornyl ketones and its conversion to substituted dihalophenols taking recourse of acid-mediated Grob fragmentation. We also propose a detailed reaction mechanism and offer evidence based on isotope labelling experiments to further support it.

**Results and discussion**

Our endeavors towards this goal began with the regioselective reduction of one of the two bridgehead halogens of easily obtainable Diels–Alder adducts 11, which was prepared according to our previously developed route.\(^{4b,d}\) It was accomplished by employing 1.5 equiv. of tri-n-butyltin hydride (TBTH) in two equal portions over a period of 2.5–3.5 h in the presence of catalytic azobisisobutyronitrile (AIBN) in refluxing benzene. Under these conditions, an appreciable conversion of the starting material 11 and a moderate yield of a chromatographically inseparable regioisomeric mixture of two mono-reduced bicyclic trihaloacetates 12 and 13 were obtained (Table 1, see also the Experimental section). However, when the mixture of acetates 12–13 was allowed to undergo hydrolysis with K₂CO₃ in MeOH, two chromatographically separable regioisomeric hydroxy compounds 15 and 16 were obtained in good overall yields (Table 2). After separation, each of 15 and 16 were separately oxidized to the corresponding bicyclic ketones 9 and 10, respectively, employing Py-CrO₃ in CH₂Cl₂ in good yields (Tables 3 and 4). Of the two regioisomeric ketones, the ones with 1-H, 10, were found to be stable at room temperature (Table 4), while the other regioisomer 9 bearing 4-H appeared to undergo decomposition at room temperature to unknown

![Scheme 1](Image) Acid-catalysed Grob fragmentation of several norbornyl ketones.

**Table 1** Regioselective mono-reduction of bridgehead halogens of tetrahalo-norbornyl acetates 11 by TBTH\(^{a,b}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, X, R</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Product/yield(^{d}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a: X = Br; R = C₆H₅</td>
<td>2.5</td>
<td>80</td>
<td>12a–13a/59</td>
</tr>
<tr>
<td>2</td>
<td>11b: X = Br; R = C₆H₅</td>
<td>3.5</td>
<td>92</td>
<td>12b–13b/60</td>
</tr>
<tr>
<td>3</td>
<td>11c: X = Br; R = Ph</td>
<td>2.5</td>
<td>82</td>
<td>12c–13c/62</td>
</tr>
<tr>
<td>4</td>
<td>11d: X = Cl; R = C₆H₅</td>
<td>3</td>
<td>77</td>
<td>12d–13d/59</td>
</tr>
</tbody>
</table>

\(^{a}\) Standard reaction conditions: 11 (1 mmol), TBTH (1.5 mmol, added in two portions), AIBN (0.05 mmol), benzene (20 mL), reflux (for details, see the Experimental section). \(^{b}\) TBTH was distilled prior to use and purity checked through GC analysis (≈95% purity). \(^{c}\) Conversion based on the recovery of the unreacted starting material 11. \(^{d}\) Isolated yield based on recovered 11.

**Table 2** Hydrolysis of trihalo-norbornyl acetates 12–13 to the corresponding alcohols 15 and 16 \(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, X, R</th>
<th>Time (h)</th>
<th>Product/yield(^{a}) (%)</th>
<th>Overall yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a–13a: X = Br; R = C₆H₅</td>
<td>24</td>
<td>15a/37, 16a/51</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>12b–13b: X = Br; R = C₆H₅</td>
<td>24</td>
<td>15b/21, 16b/65</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>12c–13c: X = Br; R = Ph</td>
<td>30</td>
<td>15c/25, 16c/60</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>12d–13d: X = Cl; R = C₆H₅</td>
<td>24</td>
<td>15d/20, 16d/68</td>
<td>88</td>
</tr>
</tbody>
</table>

\(^{a}\) Standard reaction conditions: 12–13 (0.3 mmol), K₂CO₃ (0.33 mmol), methanol (5 mL), room temperature. \(^{a}\) Isolated yield.
Oxidation of trihalo-norbornyl alcohols 15 to the corresponding ketones 9 and its acid catalysed fragmentation to halophenols 17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, X, R</th>
<th>Ketone 9/time (h)/yield (%)</th>
<th>Phenol 17/time (h)/yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15a: X = Br; R = C6H4H2</td>
<td>9a/24/86</td>
<td>17a/8/80</td>
</tr>
<tr>
<td>2</td>
<td>15b: X = Br; R = C6H4H3</td>
<td>9b/24/86</td>
<td>17b/10/82</td>
</tr>
<tr>
<td>3</td>
<td>15c: X = Br; R = Ph</td>
<td>9c/30/8d</td>
<td>17c/20/48†</td>
</tr>
<tr>
<td>4</td>
<td>15d: X = Cl; R = C6H4H2</td>
<td>9d/24/8d</td>
<td>17d/18/59†</td>
</tr>
</tbody>
</table>

Table 4 Oxidation of trihalo-norbornyl alcohols 16 to the corresponding ketones 10 and its acid catalysed fragmentation to halophenols 17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, X, R</th>
<th>Ketone 10/time (h)/yield (%)</th>
<th>Phenol 17/time (h)/yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16a: X = Br; R = C6H7</td>
<td>10a/24/88</td>
<td>17a/0.5/96</td>
</tr>
<tr>
<td>2</td>
<td>16b: X = Br; R = C6H4H3</td>
<td>10b/24/85</td>
<td>17b/0.5/92</td>
</tr>
<tr>
<td>3</td>
<td>16c: X = Br; R = Ph</td>
<td>10c/30/84</td>
<td>17c/0.5/80</td>
</tr>
<tr>
<td>4</td>
<td>16d: X = Cl; R = C6H4H2</td>
<td>10d/24/84</td>
<td>17d/1/84</td>
</tr>
</tbody>
</table>

Although both the bicyclic ketones 9 and 10 eventually afforded the same final products, however a distinct difference was observed between the reactivity of the two substrates. While the compounds 10 underwent smooth fragmentation, as observed from clean reaction mass, short reaction time as well as higher yield of 17 (Table 4), the analogous reaction of other regioisomers 9 was found to be sluggish as could be seen from the complexity of the reaction mixture, longer duration and comparatively lower yield of 17 (Table 3). These differences are clearly indicative of two distinct reaction pathways to be followed eventually leading to the same phenol derivatives 17. On the basis of our previous work and above experimental results, two plausible mechanisms have been proposed in Schemes 2 and 3.

In the presence of an acid, the carbonyl group of 9 (with 1-X and 4-H), at first, becomes protonated and subsequently follows the C1–C7 sigma bond rupture under the Grob-fragmentation pattern (route a, Scheme 2). At this stage, the resonance stabilized intermediate oxocarbenium ion 9A bearing a dienol functionality (denoted by C5–C6–C1–C2–OH), thus formed, could be hypothesized to be protonated by an external acid source from the sterically less demanding bottom face (opposed to that occupying C(OMe)3) in any one of the β or δ carbons of the dienol moiety (i.e. C-1 or C-5). Two ionic cyclohexenone derivatives i.e. 9B (via β-attack) and 9C (via δ-attack) could be the plausible intermediates (Scheme 2). In 9B, both the halogen 1-X and acidic 4-H occupy the pseudo-axial positions thus maintaining anti-periplanarity between them, the result being the easy 1,4-elimination of HX generating 9D. The products along with some amount of phenol derivatives 17 as observed from TLC monitoring as well as analysis of NMR spectra (Table 3). This in turn made it difficult to record NMR spectra of these ketones (i.e. 9) in appreciable purity. Infact compound 9c could be characterized through 1H NMR spectra only with the simultaneous presence of the corresponding phenol derivative 17c (see the Experimental section and ESI†). When the two bicyclic ketones 9 and 10 were separately treated with PTSA under refluxing toluene, surprisingly, both of them were found to generate the same dihalophenol derivatives whose structures, on the basis of 1H and 13C NMR spectral analyses, were assigned as 17 (Tables 3 and 4). Appearance of the aromatic proton 1-H in the range δ = 6.9 to 7.1 ppm in 1H NMR clearly indicates that it is positioned ortho to the OH group (see the Experimental section and ESI†); if an aromatic proton sits ortho to the ester group, the chemical shift value would be much more deshielded. Finally, the unambiguous structural proof was obtained from single crystal X-ray analysis (Fig. 1). The enormous synthetic and industrial relevance of substituted halophenols and a spectrum of bioactivities associated with them show the importance of our present method.

![Fig. 1](https://example.com/fig1.png)
the acidic proton 4-H and halogen 5-X being positioned in axial and pseudo-axial orientations, respectively, experience facile 1,2-elimination to form 9F which should generate the phenol derivative 18 in the usual manner as depicted in Scheme 2. However, in practice, only dihalophenol 17 was obtained, and no formation of its regioisomer 18 was detected as revealed from $^1$H and $^{13}$C NMR spectral analyses as well as X-ray single crystal structure. At this stage it is not clear why product formation takes place exclusively via route a and not by route b (Scheme 2).

On the other hand, in the case of substrate 10 bearing 1-H and 4-X, intermediate 10A, formed by usual protonation followed by C1–C7 sigma bond cleavage, undergoes facile removal of halogen 4-X with simultaneous reorganization of double bonds to generate the intermediate 10B (Scheme 3). The subsequent nucleophilic capture of the methyl group by X$^-$, thus liberating MeX prior to enolisation of the resulting cyclohexadienone derivative 10C explains the formation of dihalophenol 17.

Now, to check the authenticity of the proposed mechanism, two regioisomeric mono-deutero bicyclic ketones 19 and 20 (Scheme 4) were required to be prepared so as to carry out the released halide X$^-$ could then act as a nucleophile and attack the methyl carbon of the oxocarbenium ion 9D liberating gaseous methyl halide (MeX)$^{15}$ along with the cyclohexadienone moiety 9E which eventually leads to halophenol 17 through usual enolisation. Similarly in 9C (route b, Scheme 2),

**Scheme 2** Proposed mechanism for the fragmentation of norbornyl ketone 9.

**Scheme 3** Proposed mechanism for the fragmentation of norbornyl ketone 10.

**Scheme 4** Synthesis and fragmentation reaction of trihalo-norbornyl ketones 19 and 20 (bearing one bridgehead deuterium atom) in the presence of a protonated acid.
analogous rearrangement reaction over them. Substitution of one of the two bridgehead halogens of 11a with deuterium was accomplished by employing tri-n-butyltin deuteride (TBTBD)\textsuperscript{16} under previously optimized conditions (Scheme 4). A moderate yield of a chromatographically inseparable regioisomeric mixture of two mono-deuterated tribromo-bicyclic acetates 22–23 was obtained (see the Experimental section). They were converted to the corresponding bicyclic ketones 19 and 20 respectively in good overall yields via the two-step hydrolysis–oxidation strategy (Scheme 4). Both of these ketones on separate exposure to PTSA in refluxing toluene resulted in the formation of di-halophenols 26 and 27 which were found to exhibit similar types of \(^1\)H and \(^{13}\)C NMR spectra except for showing differences in the aromatic region arising from the variation in the extent of deuterium occurrence. While the phenol 26 appeared to contain only protons at C-1 of the aromatic skeleton, the predominant deuterium present at C-1 (1-D \(\sim\) 94\%, 1-H \(\sim\) 6\%) was observed in 27 (Scheme 4, also see the Experimental section and ES†).

At this juncture, to know the existence and hence to quantify the degree of deuteration in the final products obtained from the previous reactions, both \(^1\)H and \(^{13}\)C NMR spectra of compounds 26 and 27 were compared with those of the corresponding usual phenolic compound 17a (see Fig. S1 and S2 in the ES†). In fact, analysis of \(^1\)H NMR spectra revealed that phenol 27 was mostly composed of deuterium at C-1 (also supported by the corresponding \(^{13}\)C NMR spectra) but not exclusively suggesting the minor presence of hydrogen (~6\%) at C-1 as calculated on the basis of integral of the 1-H peak in the aromatic region (see the Experimental section, also see Fig. S1 and S2 in the ES†).

The observed proton/deuterium induction in the final halo-phenols 26 and 27 (Scheme 4) can be rationalized by the analogous reaction pathways as depicted in Schemes 2 and 3, respectively, the sole difference being the replacement of bridgehead hydrogens (4-H in 9, Scheme 2 and 1-H in 10, Scheme 3) by deuterium (4-D in 19 and 1-D in 20, Scheme 4, also see Fig. S3 and S4 in the ES†). Note that, starting with the bicyclic ketone 20, we can access the mono-deuterated halophenol 27 (Scheme 4). So, the present method may perhaps be applied to the synthesis of such ortho-deutero-dihalophenol derivatives 27. However, rationalization of the minor amount of proton occurrence at C-1 of 27 demands additional pathways to be invoked involving protonation at the β carbon of a dienol functionality derived from the acid-catalyzed fragmentation of 20 (analogous to 9a\(\rightarrow\)9b conversion observed in route a, Scheme 2; for further details, see Fig. S4 in the ES†).

In our previous report describing the mechanistic insight into the formation of substituted meta-halophenol derivatives,\textsuperscript{5} we already ruled out the possibility of predominant proton/deuterium incorporation in the final phenol derivatives through exchanges with the acid\textsuperscript{17} employed during the acid-mediated fragmentation of norbornyl ketones as evident from experimental observations.\textsuperscript{5} In the present report, the formation of the phenol derivative 27, predominantly deuterated at C-1, from the bicyclic ketone 20 bearing deuterium at C-1 (Scheme 4) in the presence of PTSA, clearly implies that the aforesaid exchange phenomenon has almost no contribution in the overall reaction mechanism, otherwise we would end up with 26 but not 27 due to exchanges of 1-D with protons supplied by PTSA. This observation further supports our mechanistic explanations. It is interesting to note that, if we combine the present outcome (vide supra) with our previous results (eqn (1)\textsuperscript{3} and eqn (2),\textsuperscript{5} Scheme 1) we could recognize the crucial effect of the bridgehead substituents in the overall transformation (for details, see Fig. S5 in the ES†). When the bridgehead position C-4 is occupied by a halogen (4-X in 1 and 10, Scheme 1), then irrespective of the nature of the substituent in the other bridgehead position C-1, major amounts of products are formed without necessitating the involvement of the C-1 substituent thereby retaining it in the final products (eqn (1), Scheme 1\textsuperscript{4} and Scheme 3). On the other hand, when the C-4 substituent is hydrogen (4-H in 3 and 9, Scheme 1), then the reaction pathway is dictated by the nature of the substituent at other bridgehead position C-1; if it is hydrogen (i.e. 1-H in 3, eqn (2), Scheme 1\textsuperscript{5}) then product formation takes place via exclusive protonation at δ carbon (i.e. C-5) of the dienol moiety formed in situ,\textsuperscript{3} while β carbon (i.e. C-1) would undergo similar protonation if the halogen remains at C-1 (i.e. 1-X in 9, Scheme 2). From these findings, it can be inferred that bridgehead substituents are responsible for engineering the reaction pathways to be followed and among the two substituents, one occupying the position away from the carbonyl group (i.e. C-4) has the precedence over the other located vicinal to the carbonyl moiety (i.e. C-1).

Conclusions
In conclusion, we have demonstrated the significance of bridgehead substituents in the Grob fragmentation of the appropriately functionalized norbornene skeleton, eventually allowing a new entry to substituted halophenols via judicious exploitation of the bridgehead halogens. The suitably tailored norbornyl ketone precursors, which are crucial for the present transformation, could be achieved starting from the \([4 + 2]\) cycloaddition products between the substituted vinyl acetates and 1,2,3,4-tetrahalo-5,5-dimethoxy-cyclopentadiene through the initial TBTH-mediated selective reduction of one of the two bridgehead halogens followed by basic hydrolysis prior to oxidation of the resultant norbornyl alcohols. Finally, the halophenol derivatives were obtained through an acid catalyzed Grob-fragmentation of the as-developed bicyclic ketones. The mechanistic rationale has been evidenced on the basis of deuterium labelling experiments. Although both the regioisomeric trihalo-norbornyl ketones ultimately lead to the same end products, however the mechanistic pathways involved are found to be distinctly dissimilar to each other implying crucial yet different roles played by two bridgehead substituents. When halogen occupies C-1 and hydrogen (or deuterium) at C-4, then both of them actually participate in the reaction mechanism and get knocked off as a halide ion (X") and proton (H" or
D'), respectively, the result being their absence and incorporation of H' from an external acid source within the final halophenol compound. A sharp departure from this phenomenon was observed as long as they remain in opposite orientations (1-H/D and 4-X), wherein fragmentation occurs, of course with the facile removal of the bridgehead halogen 4-X, but without any significant involvement of the bridgehead hydrogen (or deuterium) 1-H/D and hence it is retained in the end product. In the Grob fragmentation of bicyclic systems, the implication of a substitution pattern in the bridgehead positions is thus demonstrated. Moreover, the synthetic route to ortho-deutero-halophenol derivatives, as shown herein, also shows the potential application of our present method.

**Experimental**

**General methods**

All the reactions were performed in oven dried apparatus. All common reagents were obtained from commercial suppliers and used without further purification. Commercial grade solvents were distilled using standard methods. Thin layer chromatography was performed on microscope slides coated with silica gel (300 mesh). Visualization of spots was accomplished by exposure to iodine vapor and/or UV radiation and/or spraying with 4% ethanolic H2SO4 followed by charring. Column chromatography was performed using silica gel (100–200 mesh) and various combinations of ethyl acetate and hexane were used as eluents. Silver nitrate (AgNO3) impregnation of H+ from an external acid source within the final halo-halogen of tetrahalo norbornyl acetates 11 to generate a derivatization of H+ with reference to either chemical shifts (77.0 ppm) of CDCl3 (for 13C). Data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, br = broad singlet, m = multiplet). High-resolution mass spectra (HRMS) were recorded at 100 MHz unless otherwise mentioned (for 1H) and 200 MHz for 13C NMR spectra were recorded at 100 MHz unless otherwise mentioned as 125 MHz. Samples for NMR were made in CDCl3. The chemical shifts (δ ppm) and coupling constants J (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for 1H) or the central line (77.0 ppm) of CDCl3 (for 13C). Data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, m = multiplet). High-resolution mass spectra (HRMS) were recorded using either electron spray ionization (ESI) or electron ionization (EI) mode. Single crystal X-ray analysis was carried out for the structure elucidation of compound 17c (see the ESI† for full details of CIF data file).

**General procedure for reduction of one of the two bridgehead halogens of tetrahalo norbornyl acetates 11 to generate a regioisomeric mixture of 12 and 13**

1,5,6-Tribromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl acetate 12a and 4,5,6-tribromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-yl acetate 13a. To a solution of 11a (1 g, 1.75 mmol) in dry benzene (35 mL, 0.05 M) under argon, was added tri-n-butyltin hydride (TBTH) (0.38 g, 1.3 mmol, 0.75 equiv.) and AIBN (13 mg, 0.08 mmol) and the reaction mixture was refluxed under an argon atmosphere. After 1.5 h, an additional TBTH of the equal amount (0.38 g, 1.3 mmol, 0.75 equiv.) was added to the reaction mixture and was refluxed until appreciable consumption of the starting material 11a took place as revealed from TLC monitoring (another 1 h). The reaction mixture thus obtained was characterized by the simultaneous presence of a minor amount of each of unreacted 11a and dihalo acetate 14a along with a major amount of the requisite title compounds 12a–13a. The reaction mixture was then evaporated under reduced pressure to remove the solvent and the resulting crude mass was used for chromatographic separation. The tin impurities were first removed by adsorbing the oily crude mass over freshly prepared 7% AgNO3-impregnated silica gel followed by eluting with 5% EtOAc in hexane. The resulting light yellow liquid was further purified by column chromatography over silica gel by employing prolonged elution of hexane followed bycontrolled increase of the polarity of the ethyl acetate–hexane solvent system (up to 1% EtOAc in hexane as the eluent) to give back first the unreacted 11a (204 mg, 20%) and subsequently the inseparable regioisomeric trihalo acetates 12a–13a which appear as a homogeneous spot in TLC.

Rf = 0.8 [10% EtOAc in hexane (over 7% AgNO3-impregnated silica gel)]; yield 404 mg, 59% (based on the recovery of 20% unreacted 11a); viscous liquid; 1H NMR (400 MHz, CDCl3) δ 5.66 (d, J = 8.0 Hz, 1H, 2-Hexo), 5.49 (dd, J = 4.4, 8.1 Hz, 1H, 2-Hexo), 3.53 (d, J = 4.4 Hz, 1H, 1-H), 3.43 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.35 (s, 3H, OMe), 3.29 (s, 3H, OMe), 3.14 (d, J = 3.4 Hz, 1H, 4-H), 2.79–2.73 (m, 1H, 3-Hexo), 2.00 (s, 3H, OCOCH3), 2.02 (s, 3H, OCOCH3), 1.61–1.55 (m, 1H + 1H), 1.42–1.07 (a series of m, 3H + 3H), 0.90–0.87 (m, 3H + 3H); 13C NMR (100 MHz, CDCl3) δ 170.6, 170.4, 126.5, 124.2, 120.7, 113.7, 113.3, 112.9, 79.4, 75.4, 73.3, 56.3, 55.9, 53.0, 52.9, 52.4, 50.7, 50.6, 43.3, 27.8, 26.4, 21.9, 20.9, 20.6, 20.4, 14.2, 13.9; IR (neat): 2900, 1720 (C=O), 1600, 1440, 1360, 1220, 1020 cm⁻¹; Anal. Calcd for C14H19Br3O4: C, 34.25; H, 3.92. Further elution with increased solvent polarity (2% EtOAc in hexane as the eluent) resulted in the separation of the dihalo acetate 14a (127 mg, yield 22%, based on the recovery of unreacted 11a). Its spectral data are in agreement with our previous report.5

1,5,6-Tribromo-3-ethyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl acetate 12b and 4,5,6-tribromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl acetate 13b. Rf = 0.8 [10% EtOAc in hexane (over 7% AgNO3-impregnated silica gel)]; yield 474 mg, 60% from 11b (based on the recovery of 8% unreacted 11b); viscous liquid; 1H NMR (400 MHz, CDCl3) δ 5.67 (d, J = 8.1 Hz, 1H, 2-Hexo), 5.58 (dd, J = 4.3, 7.7 Hz, 1H, 2-Hexo), 3.53 (d, J = 4.2 Hz, 1H, 1-H), 3.43 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.35 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.14 (d, J = 3.6 Hz, 1H, 4-H), 2.75–2.73 (m, 1H, 3-Hexo), 2.66–2.62 (m, 1H, 3-Hexo), 2.06 (s, 3H, OCOCH3), 2.01 (s, 3H, OCOCH3), 1.59–1.56 (m, 1H + 1H), 1.27–1.22 (a series of m, 9H + 9H), 0.87–0.84 (m, 3H + 3H);
13C NMR (100 MHz, CDCl₃) δ 170.6, 170.4, 126.4, 124.1, 120.6, 112.8, 112.5, 80.2, 79.2, 78.4, 72.9, 72.8, 54.3, 54.3, 53.9, 52.6, 52.1, 50.67, 50.63, 50.59, 50.54, 49.2, 49.1, 42.8, 30.6, 29.6, 25.3, 23.5, 22.7, 22.6, 20.8, 20.7, 20.6, 20.5, 20.4, 13.9; IR (neat) 2900, 1720 (C=O), 1600, 1440, 1360, 1220, 1020 cm⁻¹.

1,5,6-Tribromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-yl acetate 12c and 4,5,6-tribromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-yl acetate 13c. R₁ = 0.6 [10% EtOAc in hexane (over 7% AgNO₃-impregnated silica gel)]; yield 442 mg, 62% from 11c (based on the recovery of 18% unreacted 11c); viscous liquid; ¹H NMR (400 MHz, CDCl₃) δ 7.60, 0.99 (s, 3H, OCOCH₃), 1.77 (s, 3H, OME); 13C NMR (100 MHz, CDCl₃) δ 123.3, 121.1, 112.9, 79.1, 56.5, 52.3, 53.2, 51.7, 27.8, 21.5, 14.1; IR (neat) 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm⁻¹; HRMS (EI) Calcd for C₁₂H₁₂Br₃O₃ [M⁺], 445.8728; Found, 445.8726.

16b. R₂ = 0.4 [10% EtOAc in hexane (over 7% AgNO₃-impregnated silica gel)]; yield 164 mg, 51% from the mixture of 12a and 13a; solid, mp 88–90 °C; ¹H NMR (400 MHz, CDCl₃) δ 4.74 (dd, J = 4.5 Hz, 7.7 Hz, 1H, 2-Hexo), 3.42 (s, 3H, OME), 3.33 (d, J = 4.4 Hz, 1H, 1-H), 3.11 (s, 3H, OME), 2.56–2.50 (m, 1H, 3-Hexo), 1.58–1.44 (m, 3H, OH peak buried under the peaks of the alkyne chain), 1.34–1.29 (m, 1H), 1.24–1.17 (m, 1H), 0.92 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 127.1, 117.4, 113.5, 75.9, 72.4, 58.8, 52.9, 51.1, 50.5, 26.0, 22.5, 14.2; IR (KBr) 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm⁻¹; HRMS (EI) Calcd for C₁₂H₁₁Br₂O₂ [M⁺], 445.8728; Found, 445.8728.

3-Butyl-1,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl acetate 12d and 3-butyl-1,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl acetate 13d. R₂ = 0.6 [7% EtOAc in hexane (over 7% AgNO₃-impregnated silica gel)]; yield 410 mg, 59% from 11d (based on the recovery of 23% unreacted 11d); viscous liquid; ¹H NMR (400 MHz, CDCl₃) δ 5.55 (d, J = 8.0 Hz, 1H, 1-H), 5.44 (dd, J = 4.4, 8.1 Hz, 1H, 2-Hexo), 3.41 (d, J = 4.39 Hz, 1H, 1-H), 3.37 (s, 3H, OME), 3.35 (s, 3H, OME), 3.29 (s, 3H, OME), 2.35 (s, 3H, OME), 2.10 (t, J = 3.7 Hz, 1H, 3-Hexo), 1.97 (s, 3H, OCOCH₃), 1.50–1.47 (m, 1H + 1H), 1.29–1.14 (m, 5H + 5H), 0.85–0.80 (m, 3H + 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 170.4, 134.5, 132.1, 132.0, 130.8, 127.9, 127.8, 127.5, 125.1, 122.2, 118.9, 113.6, 113.1, 80.8, 75.7, 74.8, 73.1, 59.3, 56.9, 56.8, 53.1, 52.6, 50.9, 49.4, 20.6, 20.4; IR (neat) 2900, 1720 (C=O), 1600, 1440, 1360, 1220, 1020 cm⁻¹; HRMS (EI) Calcd for C₁₂H₁₂Br₂O₃ [M⁺], 521.8677; Found, 521.8675.

General procedure for hydrolysis of trihalo norbornyl acetates 12–13

1,5,6-Tribromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-ol 15a and 4,5,6-tribromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-ol 16a. To a solution of 12a–13a (351 mg, 0.7 mmol) in MeOH (12 mL) was added K₂CO₃ (99 mg, 0.73 mmol) and stirred at room temperature for 24 h. After completion of the starting material (by TLC monitoring), the solvent was evaporated under reduced pressure, water (2 mL) was added to the residue and the aqueous layer was extracted thrice with EtOAc (3 x 6 mL). The combined organic layer was then washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated off in vacuo to leave a residue which was chromatographed on silica gel to afford the alcohols 15a and 16a.
1040 cm⁻¹; HRMS (EI) Caled for C₁₅H₁₉Br₃O₃ [M⁺], 479.8571; Found, 479.8570.

4,5,6-Tribromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-ol 16c. Rf = 0.3 [10% EtOAc in hexane (over 7% AgNO₃-impregnated silica gel)]; yield: 166 mg, 60% from the mixture of 12c and 13c; viscous liquid; 1H NMR (400 MHz, CDCl₃) δ 7.32–7.23 (m, 3H), 4.94 (dd, J = 4.4, 7.6 Hz, 1H, 2-Hexo), 3.80 (d, J = 7.6 Hz, 1H, 3-Hexo), 3.53 (d, J = 3.7 Hz, 1H, 1-H), 3.52 (s, 3H, OMe), 3.38 (s, 3H, OMe), 1.54 (brs, 1H, OH); 13C NMR (100 MHz, CDCl₃) δ 132.4 (2C), 132.1, 128.0 (3C), 127.1, 119.8, 113.8, 76.1, 73.6, 58.7, 57.9, 53.0, 50.6; IR (KBr) 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm⁻¹; Anal. Caled for C₁₂H₁₂Br₃O₃: C, 54.4, 52.0, 50.5, 42.9, 30.3, 25.2, 22.7, 14.0; IR (neat) 3400 (OH), 2900, 1600, 1440, 1240, 1060 cm⁻¹; HRMS (EI) Caled for C₁₂H₁₂Br₃O₃ [M⁺], 443.8571; Found, 443.8573.

1,5,6-Tribromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 10b. Rf = 0.7 [10% EtOAc in hexane (over 7% AgNO₃-impregnated silica gel)]; yield 46 mg, 86% from alcohol 15b; viscous liquid; 1H NMR (400 MHz, CDCl₃) δ 3.49 (s, 3H, OMe), 3.46 (d, J = 3.4 Hz, 1H, 4-H), 3.34 (s, 3H, OMe), 2.56–2.52 (m, 1H, 3-Hexo), 1.84–1.75 (m, 1H), 1.46–1.23 (m, 9H), 0.86 (t, J = 6.4 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 200.4, 126.3, 120.3, 115.7, 79.1, 54.3, 52.9, 50.9, 45.3, 31.5, 28.8, 28.6, 27.8, 22.5, 14.0; IR (neat) 2900, 1740 (C=O), 1580, 1440, 1200, 1100, 960 cm⁻¹.

1,5,6-Tribromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 10c. Rf = 0.8 [10% EtOAc in hexane (over 7% AgNO₃-impregnated silica gel)]; yield 100 mg, 84% from alcohol 16c; solid, mp 82–84 °C; 1H NMR (400 MHz, CDCl₃) δ 3.51 (s, 3H, OMe), 3.42 (s, 1H), 3.36 (s, 3H, OMe), 2.63 (dd, J = 5.1 Hz, 8.7 Hz, 1H, 3-Hexo), 1.74–1.52 (m, 3H), 1.44–1.35 (m, 1H), 0.91 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 202.5, 131.7, 115.8, 113.0, 71.9, 67.6, 53.3, 52.6, 50.9, 29.9, 21.6, 13.9; IR (KBr) 2900, 1740 (C=O), 1600, 1440, 1200, 1100, 960 cm⁻¹; HRMS (EI) Caled for C₁₃H₁₁Br₃O₃ [M⁺], 485.9041; Found, 485.9042.

General procedure for oxidation of alcohols 15 and 16

1,5,6-Tribromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-ol 16d. Rf = 0.4 [7% EtOAc in hexane (over 7% AgNO₃-impregnated silica gel)]; yield: 181 mg, 68% from the mixture of 12d and 13d; solid, mp 74–76 °C; 1H NMR (400 MHz, CDCl₃) δ 4.67 (dd, J = 4.7, 7.5 Hz, 1H, 2-Hexo), 3.35 (s, 3H, OMe), 3.26 (s, 3H, OMe), 3.19 (d, J = 4.4 Hz, 1H, 1-H), 2.43–2.37 (m, 1H, 3-Hexo), 1.48–1.03 (m, 7H, OH peak buried under the peaks of 6H of the alkyl chain), 0.84 (t, J = 6.7 Hz, 3H); 13C NMR (100 MHz, CDCl₃) δ 130.7, 125.2, 113.1, 80.5, 71.7, 56.8, 52.6, 50.5, 50.1, 31.3, 23.2, 22.9, 13.9; IR (KBr) 3500 (OH), 2900, 1600, 1440, 1240, 1020, 980 cm⁻¹; Anal. Caled for C₁₇H₁₄Br₅O₃: C, 47.37; H, 5.81. Found: C, 47.32; H, 5.73.

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3-Butyl-1,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 9d (due to slow decomposition, apart from peaks characteristic of 9d, some undefined peaks are also observed).  

**General procedure for fragmentation of ketones 10 to substituted dihalophenals 17**  

**Methyl 2,3-dibromo-5-hydroxy-6-propylbenzoate 17a.** To a solution of the ketone 9a (80 mg, 0.18 mmol) in toluene (6 mL) was added para-toluenesulphonic acid monohydrate (PTSA) (60 mg, 0.32 mmol) and the reaction mixture was heated to reflux at 110–120 °C for 8 h. The end of the reaction was monitored by TLC with the disappearance of the ketone 9a. The reaction mixture was diluted with water (4 mL) and the aqueous layer was extracted thrice with EtOAc (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na2SO4. The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography to afford the methyl 5-bromo-5-hydroxy-2-propylbenzoate 17a.

**Methyl 2,3-dibromo-5-hydroxy-6-hexyl-5-hydroxybenzoate 17b (from 9b).**  

**Methyl 3,4-dibromo-5-hydroxyphenyl-2-carboxylate 17c (from 9c).**  

**Methyl 2-butyl-5,6-dichloro-3-hydroxybenzoate 17d (from 9d).**  

**General procedure for fragmentation of ketones 10 to substituted dihalophenals 17**  

The procedure remains the same as that of ketone 6 except that both the amount of acid (1 equiv.) and the reaction time (0.5 h) were found to be less here compared to the former.
Methyl 2-butyl-5,6-dichloro-3-hydroxybenzoate 17d (from 10d). \( R_t = 0.5 \) [7% EtOAc in hexane (over 7% AgNO\(_3\)-impregnated silica gel)]; yield 60 mg, 84% from ketone 10d; crystalline solid, mp 64–66 °C. It shows similar spectral data.

1,5,6-Tribromo-4-deutero-7,7-dimethoxy-3-propylbicyclo-[2.2.1]hept-5-en-2-yl acetate 22 and 4,5,6-tribromo-1-deutero-7,7-dimethoxy-3-propylbicyclo-[2.2.1]hept-5-en-2-yl acetate 23. \( R_t = 0.8 \) [10% EtOAc in hexane (over 7% AgNO\(_3\)-impregnated silica gel)]; yield 88 mg, 88% from alcohol 25; solid, mp 82–84 °C; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 3.52 (s, 3H, OMe), 3.37 (s, 3H, OMe), 2.63 (dd, \( J = 5.2, 8.2 \) Hz, 1H, 3-Hexo), 1.72–1.63 (m, 1H), 1.61–1.54 (m, 2H), 1.44–1.38 (m, 1H), 0.92 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 201.4, 160.0, 1440, 1200, 1100, 960 cm\(^{-1}\); HRMS (ESI) Calcd for \( \text{C}_{11}\text{H}_{11}\text{DBr}_2\text{O}_3 \) [M + H\(^+\)], 399.9382; Found, 399.9386.

Dibromophenol derivative 26 \( f = 0.4 \) [10% EtOAc in hexane (over 7% AgNO\(_3\)-impregnated silica gel)]; yield 25 mg, 80% from ketone 19; solid, mp 98–100 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.11 (s, 1H), 3.95 (s, 3H, OMe), 2.46 (t, \( J = 7.9 \) Hz, 2H), 1.59–1.53 (m, 2H), 0.94 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 163.8, 153.8, 138.5, 127.7, 122.7, 120.9, 111.8, 52.9, 30.6, 22.8, 14.3; IR (KBr) 3200 (OH), 2900, 1700 (C=O), 1560, 1440, 1260, 1060 cm\(^{-1}\); HRMS (ESI) Calcd for \( \text{C}_{11}\text{H}_{11}\text{DBr}_2\text{O}_3 \) [M + H\(^+\)], 350.9231; Found, 350.9231.

Dibromophenol derivative 27 \( f = 0.1 \) [10% EtOAc in hexane (over 7% AgNO\(_3\)-impregnated silica gel)]; yield 41 mg, 96% from ketone 20; solid, mp 98–100 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.09 (s, 1H, 4-H from the minor component), 3.96 (s, 3H, OMe), 2.45 (t, \( J = 7.9 \) Hz, 2H), 1.59–1.50 (m, 2H), 0.93 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 168.4, 153.7, 138.2, 127.7, 122.5, 120.8–120.4 (m, C-4 attached to D), 111.5, 52.9, 30.5, 22.7, 14.2; IR (KBr) 3200 (OH), 2900, 1700 (C=O), 1560, 1440, 1260, 1060 cm\(^{-1}\); HRMS (ESI) Calcd for \( \text{C}_{11}\text{H}_{11}\text{DBr}_2\text{O}_3 \) [M + H\(^+\)], 350.9231; Found, 350.9231.

Acknowledgements

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Notes and references

3 For representative examples on the synthetic utility of Grob fragmentation, see: (a) G. Lemonnier and A. B. Charette, J. Org. Chem., 2012, 77, 5832–5837; (b) R. M. Oetterli,
Comparison of chemical shift values of the aromatic carbons (Scheme 1) obtained via our previously reported methodology supports our justification.

Crystallographic data (excluding structure factors) for the structure 17c have been deposited with the Cambridge Crystallographic Data Centre as the supplementary publication number CCDC 1404444.


14 For clarity, identical numbering order as for 9 is maintained for other intermediates as well as the final phenol derivatives formed. Hence, the numbering sequence of the final phenols is different in the Results and discussion section compared to those in the Experimental section wherein numbering based on a conventional priority order (i.e. as obtained from Chemdraw) is carried out.

15 Release of gaseous MeX had already been proved unambiguously in our previous work through trapping of MeBr via $^1$H NMR.


18 Herein, for the nomenclature of final dihalophenols 17, 26 and 27, the aromatic carbons are numbered on the basis of a conventional priority order (i.e. as obtained from Chemdraw), and hence they are different with respect to those used in the Results and discussion section.