Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2015, **13**, 9686

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

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Received 24th June 2015,
Accepted 4th August 2015

DOI: 10.1039/c5ob01287b

www.rsc.org/obc

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.[1,2] 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.[3] 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, **2** and **4** (also **5**) from the acid-catalysed fragmentation of tetrahalo- and dihalo-bicyclic ketones **1** and **3**, respectively (eqn (1) and (2), Scheme 1).[4,5] Both compounds **1** and **3** (eqn (1) and (2), Scheme 1),[4,5] 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[1,2] 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.[4,5] This strategy was further employed on norbornyl α-diketones **6** eventually affording substituted aromatic compounds **8** *via* the intermediate formation of α-ketoenols **7** (eqn (3), Scheme 1).[6] Since there is no example in the literature on regiospecific utilization of two bridgehead

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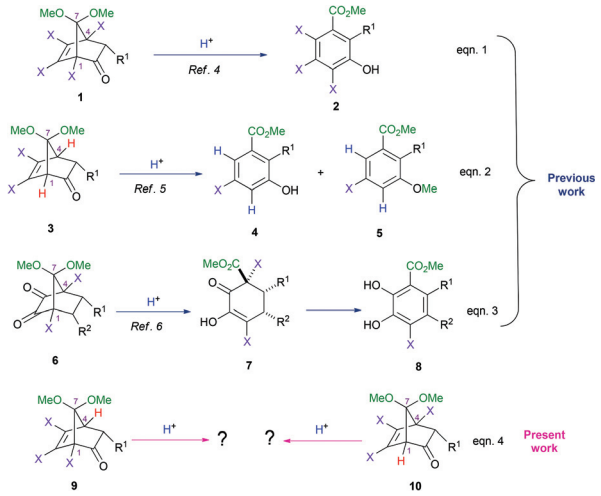
†Electronic supplementary information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds, relevant discussions and X-ray data for **17c** (CIF). CCDC 1404444. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob01287b



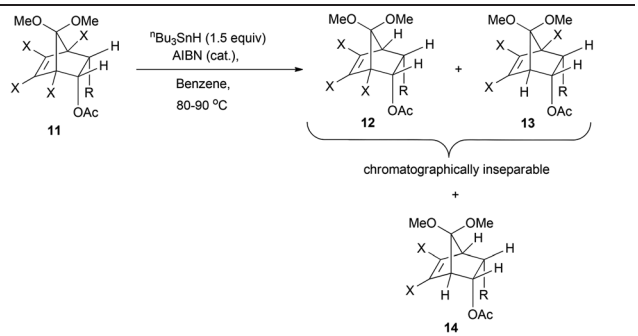
Scheme 1 Acid-catalysed Grob fragmentation of several norbornyl ketones.

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,c] 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 K_2CO_3 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–CrO_3 in CH_2Cl_2 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

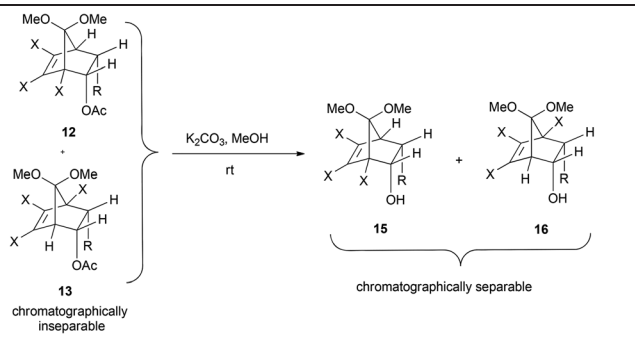
Table 1 Regioselective mono-reduction of bridgehead halogens of tetrahalo-norbornyl acetates **11** by TBTH[a,b]



Entry	Substrate, X, R	Time (h)	Conversion[c] (%)	Product/yield[d] (%)	
1	**11a**: X = Br; R = $^nC_3H_7$	2.5	80	**12a–13a**/59	**14a**/22
2	**11b**: X = Br; R = $^nC_6H_{13}$	3.5	92	**12b–13b**/60	**14b**/21
3	**11c**: X = Br; R = Ph	2.5	82	**12c–13c**/62	**14c**/18
4	**11d**: X = Cl; R = $^nC_4H_9$	3	77	**12d–13d**/59	**14d**/20

[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**.

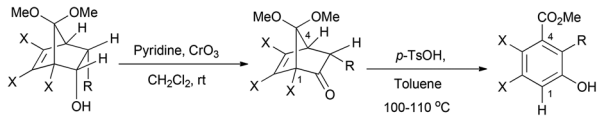
Table 2 Hydrolysis of trihalo-norbornyl acetates **12–13** to the corresponding alcohols **15** and **16** [a]



Entry	Substrate, X, R	Time (h)	Product/yield[b] (%)	Overall yield (%)
1	**12a–13a**: X = Br; R = $^nC_3H_7$	24	**15a**/37, **16a**/51	88
2	**12b–13b**: X = Br; R = $^nC_6H_{13}$	24	**15b**/21, **16b**/65	86
3	**12c–13c**: X = Br; R = Ph	30	**15c**/25, **16c**/60	85
4	**12d–13d**: X = Cl; R = $^nC_4H_9$	24	**15d**/20, **16d**/68	88

[a] Standard reaction conditions: **12–13** (0.3 mmol), K_2CO_3 (0.33 mmol), methanol (5 mL), room temperature. [b] Isolated yield.

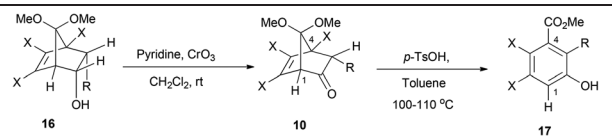
Table 3 Oxidation of trihalo-norbornyl alcohols **15** to the corresponding ketones **9**[a] and its acid catalysed fragmentation to halophenols **17**[b]



Entry	Substrate, X, R	Ketone **9**/time (h)/yield[c] (%)	Phenol **17**/time (h)/yield[c] (%)
1	**15a**: X = Br; R = $^{n}C_3H_7$	**9a**/24/86	**17a**/8/80
2	**15b**: X = Br; R = $^{n}C_6H_{13}$	**9b**/24/86	**17b**/10/82
3	**15c**: X = Br; R = Ph	**9c**/30/[d]	**17c**/20/48[e]
4	**15d**: X = Cl; R = $^{n}C_4H_9$	**9d**/24/[d]	**17d**/18/59[e]

[a] Standard reaction conditions: **15** (0.1 mmol), pyridine (1.33 mmol), CrO_3 (0.66 mmol), dichloromethane (4 mL), room temperature. [b] Standard reaction conditions: **9** (0.1 mmol), PTSA (0.18 mmol), toluene (3 mL), reflux. [c] Isolated yield. [d] Yield could not be calculated correctly due to decomposition of **9c** and **9d** to unknown products (including some **17c** for **9c** as revealed from the NMR study, see the Experimental section and ESI). [e] Overall yield for two steps (*i.e.* from **15c** and **15d** respectively); starting materials **9c** and **9d** decomposed partially.

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



Entry	Substrate, X, R	Ketone **10**/time (h)/yield[c] (%)	Phenol **17**/time (h)/yield[c] (%)
1	**16a**: X = Br; R = $^{n}C_3H_7$	**10a**/24/88	**17a**/0.5/96
2	**16b**: X = Br; R = $^{n}C_6H_{13}$	**10b**/24/85	**17b**/0.5/92
3	**16c**: X = Br; R = Ph	**10c**/30/84	**17c**/0.5/80
4	**16d**: X = Cl; R = $^{n}C_4H_9$	**10d**/24/84	**17d**/1/84

[a] Standard reaction conditions: **16** (0.1 mmol), pyridine (1.33 mmol), CrO_3 (0.66 mmol), dichloromethane (4 mL), room temperature. [b] Standard reaction conditions: **10** (0.1 mmol), PTSA (0.1 mmol), toluene (3 mL), reflux. [c] Isolated yield.

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 ^{1}H 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 ^{1}H and ^{13}C 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 [7] in ^{1}H 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.[8] Finally, the unambiguous structural proof was obtained from single crystal X-ray analysis (Fig. 1).[9] The enormous synthetic and industrial relevance of substituted halophenols and a spectrum of bioactivities associated with them show the importance of our present method.[10–13]

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[4,5] 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),[14] thus formed, could be hypothesized to be protonated by an external acid source from the sterically less demanding bottom face (opposed to that occupying $C(OMe)_2^{+}$) 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

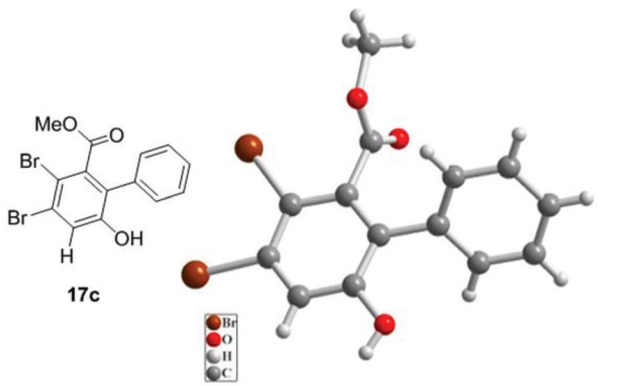
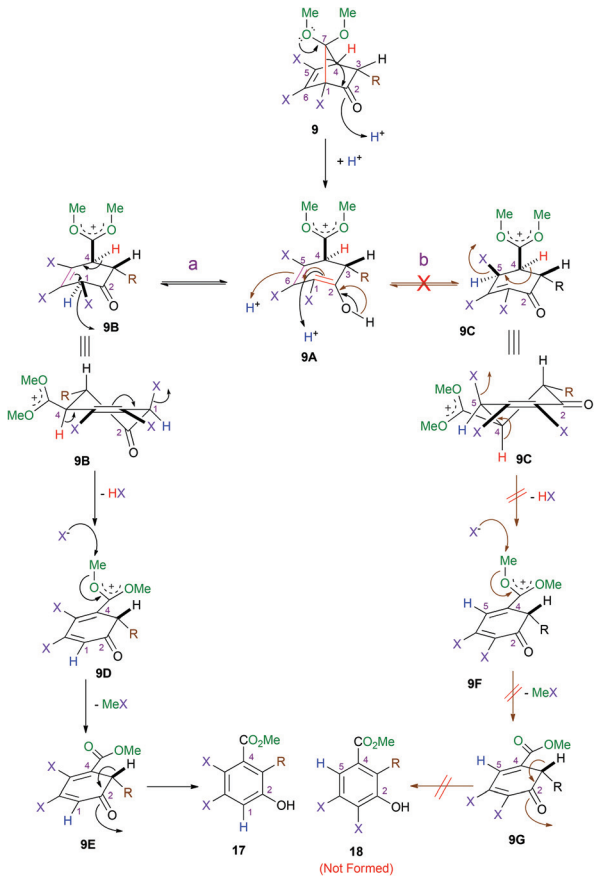
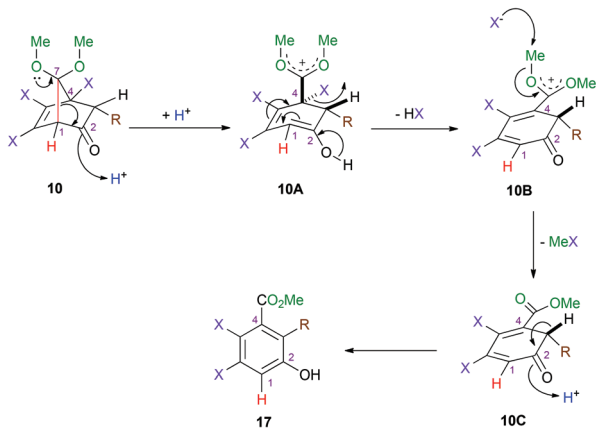


Fig. 1 X-ray crystal structure of compound **17c**. C, O, H, Br are represented by black, red, grey and brown respectively.



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

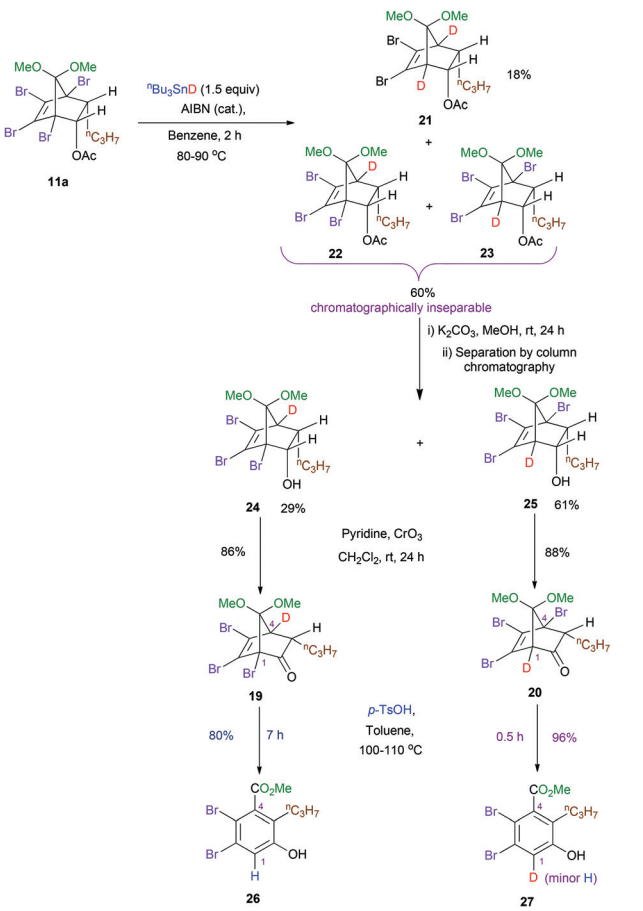


Scheme 3 Proposed mechanism for the fragmentation of norbornyl ketone **10**.

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), 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



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 (TBTD)[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 ~ 94%, 1-H ~ 6%) was observed in **27** (Scheme 4, also see the Experimental section and ESI†).

At this juncture, to know the existence and hence to quantitate 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 ESI†). 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 ESI†).

The observed proton/deuterium induction in the final halophenols **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 ESI†). Note that, starting with the bicyclic ketone **20**, we can access the mono-deutero 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→9B** conversion observed in route a, Scheme 2; for further details, see Fig. S4 in the ESI†).

In our previous report describing the mechanistic insight into the formation of substituted *meta*-halophenol derivatives,[5] we already ruled out the possibility of predominant proton/deuterium incorporation in the final phenol derivatives through exchanges with the acid[17] employed during the acid-mediated fragmentation of norbornyl ketones as evident from experimental observations.[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)[4] and eqn (2),[5] Scheme 1) we could recognize the crucial effect of the bridgehead substituents in the overall transformation (for details, see Fig. S5 in the ESI†). 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[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[5]) then product formation takes place *via* exclusive protonation at δ carbon (*i.e.* C-5) of the dienol moiety formed *in situ*,[5] 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*-deuterohalophenol 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 H_2SO_4 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 ($AgNO_3$) impregnated silica gel for column chromatography was prepared by mixing silica gel and 7 wt% of $AgNO_3$ in a minimum amount of water sufficient to generate a homogeneous slurry followed by evaporation of water on heating and subsequent drying overnight in an oven. Melting points reported are uncorrected. IR spectra were recorded as KBr pellets (solids) or thin films (liquids). ^{1}H NMR spectra were recorded at 400 MHz unless otherwise mentioned as 500 MHz. Proton-decoupled ^{13}C NMR spectra were recorded at 100 MHz unless otherwise mentioned as 125 MHz. Samples for NMR were made in $CDCl_3$. The chemical shifts (δ ppm) and coupling constants J (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for ^{1}H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). 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-7,7-dimethoxy-3-propylbicyclo[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% $AgNO_3$-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 by controlled 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.

R_f = 0.8 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 404 mg, 59% (based on the recovery of 20% unreacted **11a**); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (d, J = 8.0 Hz, 1H, 2-H_{exo}), 5.49 (dd, J = 4.4, 8.1 Hz, 1H, 2-H_{exo}), 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-H_{exo}), 2.68–2.64 (m, 1H, 3-H_{exo}), 2.06 (s, 3H, $OCOCH_3$), 2.02 (s, 3H, $OCOCH_3$), 1.61–1.55 (m, 1H + 1H), 1.42–1.07 (a series of m, 3H + 3H), 0.90–0.87 (m, 3H + 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 126.5, 124.2, 120.7, 117.7, 113.3, 112.9, 79.4, 75.4, 73.3, 56.3, 55.9, 52.9, 52.4, 50.7, 50.6, 50.3, 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 $C_{14}H_{19}Br_3O_4$: C, 34.25; H, 3.90. Found: C, 34.48; 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-hexyl-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. R_f = 0.8 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 474 mg, 60% from **11b** (based on the recovery of 8% unreacted **11b**); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (d, J = 8.1 Hz, 1H, 2-H_{exo}), 5.58 (dd, J = 4.3, 7.7 Hz, 1H, 2-H_{exo}), 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-H_{exo}), 2.66–2.62 (m, 1H, 3-H_{exo}), 2.06 (s, 3H, $OCOCH_3$), 2.01 (s, 3H, $OCOCH_3$), 1.59–1.56 (m, 1H + 1H), 1.27–1.22 (a series of m, 9H + 9H), 0.87–0.84 (m, 3H + 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 126.4, 124.1, 120.6, 117.6, 113.2, 112.8, 79.3, 75.3, 73.3, 56.1, 55.8, 52.9, 52.4, 50.7, 50.5, 50.4, 43.5, 31.6, 29.4, 29.2, 28.6, 27.7, 25.7, 24.2, 22.5, 20.7, 20.4; 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-phenylbicyclo[2.2.1]hept-5-en-2-yl acetate 13c. R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 442 mg, 62% from **11c** (based on the recovery of 18% unreacted **11c**); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.17 (m, 3H + 3H), 7.10–7.05 (m, 2H + 2H), 5.72 (d, J = 8.3 Hz, 1H, 2-H_{exo}), 5.69 (dd, J = 4.8, 8.2 Hz, 1H, 2-H_{exo}), 3.99 (dd, J = 3.8 Hz, 7.9 Hz, 1H, 3-H_{exo}), 3.89 (d, J = 8.03 Hz, 1H, 3-H_{exo}), 3.53 (d, J = 4.2 Hz, 1H, 1-H), 3.49 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.32 (s, 3H, OMe), 3.19 (d, J = 3.7 Hz, 1H, 4-H), 1.77 (s, 3H, $OCOCH_3$), 1.75 (s, 3H, $OCOCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 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, 50.7, 49.4, 20.6, 20.4; IR (neat) 2900, 1720 (C=O), 1600, 1440, 1360, 1220, 1020 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{17}Br_3O_4$ $[M]^+$, 521.8677; Found, 521.8675.

3-Butyl-1,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl acetate 12d and 3-butyl-4,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl acetate 13d. R_f = 0.6 [7% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 410 mg, 59% from **11d** (based on the recovery of 23% unreacted **11d**); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (d, J = 8.0 Hz, 1H, 2-H_{exo}), 5.44 (dd, J = 4.4, 8.1 Hz, 1H, 2-H_{exo}), 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), 3.25 (s, 3H, OMe), 3.04 (d, J = 3.6 Hz, 1H, 4-H), 2.71–2.64 (m, 1H, 3-H_{exo}), 2.57–2.52 (m, 1H, 3-H_{exo}), 2.01 (s, 3H, $OCOCH_3$), 1.97 (s, 3H, $OCOCH_3$), 1.50–1.47 (m, 1H + 1H), 1.29–1.14 (m, 5H + 5H), 0.85–0.80 (m, 3H + 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.4, 130.3, 128.1, 127.9, 125.2, 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}; HRMS (EI) Calcd for $C_{15}H_{21}Cl_3O_4$ $[M]^+$, 370.0505; Found, 370.0502.

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 K_2CO_3 (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 × 6 mL). The combined organic layer was then washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated off *in vacuo* to leave a residue which was chromatographed on silica gel to afford the alcohols **15a** and **16a**.

15a: R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 120 mg, 37% from the mixture of **12a** and **13a**; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (d, J = 8.0 Hz, 1H, 2-H_{exo}), 3.38 (s, 3H, OMe), 3.35 (s, 3H, OMe), 3.11 (d, J = 3.7 Hz, 1H, 4-H), 2.64–2.57 (m, 1H, 3-H_{exo}), 1.64 (brs, 1H, OH), 1.44–1.13 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.3, 121.1, 112.9, 79.1, 56.5, 52.3, 50.5, 43.3, 27.8, 21.5, 14.1; IR (neat) 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm^{-1}; HRMS (EI) Calcd for $C_{12}H_{17}Br_3O_3$ $[M]^+$, 445.8728; Found, 445.8726.

16a: R_f = 0.4 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 164 mg, 51% from the mixture of **12a** and **13a**; solid, mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (dd, J = 4.5 Hz, 7.7 Hz, 1H, 2-H_{exo}), 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-H_{exo}), 1.58–1.44 (m, 3H, OH peak buried under the peaks of 2H of the alkyl chain), 1.34–1.29 (m, 1H), 1.24–1.17 (m, 1H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{12}H_{17}Br_3O_3$ $[M]^+$, 445.8728; Found, 445.8728.

1,5,6-Tribromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol 15b. R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 62 mg, 21% from the mixture of **12b** and **13b**; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (d, J = 8.0 Hz, 1H, 2-H_{exo}), 3.37 (s, 3H, OMe), 3.35 (s, 3H, OMe), 3.11 (d, J = 3.6 Hz, 1H, 4-H), 2.59–2.55 (m, 1H, 3-H_{exo}), 1.70 (brs, 1H, OH), 1.39–1.16 (m, 10H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.3, 121.1, 112.9, 79.1, 76.9, 56.3, 52.3, 50.5, 43.5, 31.7, 29.3, 28.2, 25.6, 22.6, 14.0; IR (neat) 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{23}Br_3O_3$ $[M]^+$, 487.9197; Found, 487.9195.

4,5,6-Tribromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol 16b. R_f = 0.4 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 192 mg, 65% from the mixture of **12b** and **13b**; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (dd, J = 4.4 Hz, 6.5 Hz, 1H, 2-H_{exo}), 3.42 (s, 3H, OMe), 3.32 (d, J = 4.6 Hz, 1H, 1-H), 3.31 (s, 3H, OMe), 2.53–2.49 (m, 1H, 3-H_{exo}), 1.61–1.43 (m, 3H, OH peak buried under the peaks of 2H of the alkyl chain), 1.28–1.26 (m, 8H), 0.86 (t, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.9, 117.4, 113.4, 75.9, 72.3, 58.6, 52.9, 51.2, 50.5, 31.7, 29.5, 29.4, 23.9, 22.6, 14.1; IR (KBr) 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{23}Br_3O_3$ $[M]^+$, 487.9197; Found, 487.9196.

1,5,6-Tribromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-ol 15c. R_f = 0.5 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 68 mg, 25% from the mixture of **12c** and **13c**; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.18 (m, 5H), 4.79 (d, J = 8.1 Hz, 1H, 2-H_{exo}), 3.85 (dd, J = 3.6, 7.8 Hz, 1H, 3-H_{exo}), 3.44 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.21 (d, J = 3.7 Hz, 1H, 4-H), 1.69 (brs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 131.3 (2C), 128.1 (2C), 127.5, 125.2, 121.7, 113.1, 80.0, 59.3, 52.5, 50.8, 49.5 (one bridgehead C buried under the peaks of $CDCl_3$ between δ 77.3 and 76.7 ppm); IR (neat) 3400 (OH), 2900, 1580, 1440, 1240,

1040 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{15}Br_3O_3$ $[M]^+$, 479.8571; Found, 479.8570.

4,5,6-Tribromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-ol 16c. R_f = 0.3 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield: 166 mg, 60% from the mixture of **12c** and **13c**; viscous liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.23 (m, 5H), 4.94 (dd, J = 4.4, 7.6 Hz, 1H, 2-H_{exo}), 3.80 (d, J = 7.6 Hz, 1H, 3-H_{exo}), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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. Calcd for $C_{15}H_{15}Br_3O_3$: C, 37.30; H, 3.13. Found: C, 37.29; H, 3.10.

3-Butyl-1,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol 15d. R_f = 0.6 [7% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 54 mg, 20% from the mixture of **12d** and **13d**; viscous liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, J = 8.1 Hz, 1H, 2-H_{exo}), 3.35 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.03 (d, J = 3.7 Hz, 1H, 4-H), 2.59–2.52 (m, 1H, 3-H_{exo}), 1.76 (brs, 1H, OH), 1.45–1.09 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.2, 127.5, 112.5, 81.7, 78.0, 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) Calcd for $C_{13}H_{19}Cl_3O_3$ $[M]^+$, 328.0400; Found, 328.0401.

3-Butyl-4,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol 16d. R_f = 0.4 [7% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield: 181 mg, 68% from the mixture of **12d** and **13d**; solid, mp 74–76 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (dd, J = 4.7, 7.5 Hz, 1H, 2-H_{exo}), 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-H_{exo}), 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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. Calcd for $C_{13}H_{19}Cl_3O_3$: C, 47.37; H, 5.81. Found: C, 47.32; H, 5.73.

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-one 9a. To a solution of pyridine (236 mg, 2.98 mmol) in CH_2Cl_2 (4 mL) was added CrO_3 (148 mg, 1.48 mmol) and the mixture was stirred at room temperature for 30 min. To this deep brown colored mixture was added a solution of the alcohol **15a** (100 mg, 0.22 mmol) in CH_2Cl_2 (4 mL) and the mixture was stirred at room temperature for 24 h. The reaction mixture was then filtered off through a small silica gel pad to remove the inorganic impurities and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography to furnish the corresponding bicyclic ketone **9a**. R_f = 0.7 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 84 mg, 86% from **15a**; viscous liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 3H, OMe), 3.46 (d, J = 3.9 Hz, 1H, 4-H), 3.34 (s, 3H, OMe), 2.58–2.54 (m, 1H, 3-H_{exo}), 1.81–1.72 (m, 1H), 1.49–1.39 (m, 2H), 1.27–1.24 (m, 1H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 126.3, 120.4, 115.8, 79.2, 55.5, 52.3, 50.9, 45.1, 30.6, 21.2, 13.6; IR (neat) 2900, 1740 (C═O), 1580, 1440, 1200, 1100, 960 cm^{-1}.

4,5,6-Tribromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-one 10a. R_f = 0.8 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 120 mg, 88% from alcohol **16a**; solid, mp 82–84 °C; ^1H NMR (400 MHz, $CDCl_3$) 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-H_{exo}), 1.74–1.52 (m, 3H), 1.44–1.35 (m, 1H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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) Calcd for $C_{12}H_{15}Br_3O_3$ $[M]^+$, 443.8571; Found, 443.8573.

1,5,6-Tribromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 9b. R_f = 0.7 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 46 mg, 86% from alcohol **15b**; viscous liquid; ^1H NMR (400 MHz, $CDCl_3$) 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-H_{exo}), 1.84–1.75 (m, 1H), 1.46–1.23 (m, 9H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 126.3, 120.3, 115.7, 79.1, 55.4, 52.3, 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}.

4,5,6-Tribromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 10b. R_f = 0.8 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 147 mg, 85% from alcohol **16b**; solid, mp 46–48 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 3H, OMe), 3.40 (s, 1H, 1-H), 3.36 (s, 3H, OMe), 2.61 (dd, J = 4.5, 7.7 Hz, 1H, 3-H_{exo}), 1.64–1.27 (m, 10H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 131.7, 115.8, 112.9, 71.9, 67.5, 53.4, 52.8, 50.9, 31.5, 29.2, 28.3, 27.9, 22.6, 14.1; IR (KBr) 2900, 1740 (C═O), 1600, 1440, 1200, 1100, 960 cm^{-1}; Anal. Calcd for $C_{15}H_{21}Br_3O_3$: C, 36.84; H, 4.33. Found: C, 37.19; H, 4.41; HRMS (EI) Calcd for $C_{15}H_{21}Br_3O_3$ $[M]^+$, 485.9041; Found, 485.9042.

1,5,6-Tribromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-one 9c (along with methyl 3,4-dibromo-6-hydroxybiphenyl-2-carboxylate 17c; the ketone 9c underwent slow decomposition to phenol 17c during reaction as well as in separation from column). R_f = 0.6 for **9c** and 0.4 for **17c** [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; viscous liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.23 (m, 9H, Ar–H), 6.98–6.96 (m, 2H, Ar–H), 4.04 (d, J = 3.7 Hz, 1H, 3-H_{exo} of **9c**), 3.61 (d, J = 3.7 Hz, 1H, 4-H of **9c**), 3.56 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.38 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7 (C═O of **9c**), 166.3 (C═O of **17c**), 151.7, 134.7, 134.5, 131.7, 129.2, 128.9, 128.8, 128.7, 128.6, 128.3, 127.9, 127.4, 126.1, 124.4, 119.9, 117.2, 115.0, 77.9, 58.9, 52.5, 52.4, 51.3, 50.2.

4,5,6-Tribromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-one 10c. R_f = 0.7 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 100 mg, 84% from alcohol **16c**; solid, mp 144–146 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28 (m, 3H), 7.00–6.98 (m, 2H), 4.01 (s, 1H, 3-H_{exo}), 3.69 (s, 1H, 1-H), 3.62 (s, 3H, OMe), 3.44 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.8, 132.72, 132.67, 130.4 (2C), 128.4 (2C), 128.3,

115.3, 112.5, 73.2, 68.2, 58.5, 53.6, 51.3; IR (KBr) 2900, 1740 (C═O), 1600, 1440, 1200, 1100, 960 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{13}Br_3O_3$ $[M]^+$, 477.8415; Found, 477.8417.

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). R_f = 0.7 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; viscous liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H, OMe), 3.29 (broad peak, 4H, one OMe peak overlapped with the 4-H peak), 2.51–2.48 (m, 1H, 3-H_{exo}), 1.76–1.74 (m, 1H), 1.28–1.18 (m, 5H), 0.84 (t, J = 7.0 Hz, 3H).

3-Butyl-4,5,6-trichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one 10d. R_f = 0.9 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 117 mg, 84% from alcohol **16d**; solid, mp 82–84 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.44 (s, 3H, OMe), 3.33 (s, 1H, 1-H), 3.32 (s, 3H, OMe), 2.55 (dd, J = 5.7 Hz, 7.2 Hz, 1H), 1.55–1.39 (m, 4H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 135.0, 121.5, 115.6, 77.9, 65.2, 53.1, 51.9, 51.1, 30.3, 27.3, 22.6, 13.7; IR (KBr) 2900, 1740 (C═O), 1600, 1440, 1200, 1100, 960 cm^{-1}; Anal. Calcd for $C_{13}H_{17}Cl_3O_3$: C, 47.66; H, 5.23. Found: C, 47.72; H, 5.27.

General procedure for fragmentation of ketones 9 to substituted dihalophenols 17 [18]

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 Na_2SO_4. The solvent was concentrated *in vacuo* to furnish a residue which was purified by silica gel column chromatography to afford the methyl 5-bromo-3-hydroxy-2-propylbenzoate **17a**.

17a (from 9a). R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 50 mg, 80%; crystalline solid, mp 98–100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 3.93 (s, 3H, OMe), 2.43 (t, J = 7.9 Hz, 2H), 1.56–1.50 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 153.6, 138.5, 127.6, 122.7, 120.9, 111.6, 52.9, 30.5, 22.7, 14.2; IR (KBr) 3200 (OH), 2900, 1700 (C═O), 1560, 1440, 1400, 1260, 1200, 1060 cm^{-1}; Anal. Calcd for $C_{11}H_{12}Br_2O_3$: C, 37.53; H, 3.44. Found: C, 37.60; H, 3.41.

General procedure for fragmentation of ketones 10 to substituted dihalophenols 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 2,3-dibromo-5-hydroxy-6-propylbenzoate 17a (from 10a). R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 60 mg, 96% from ketone **10a**; solid, mp 98–100 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 3.93 (s, 3H, OMe), 2.43 (t, J = 7.9 Hz, 2H), 1.56–1.50 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 153.7, 138.3, 127.6, 122.6, 120.9, 111.6, 52.9, 30.5, 22.7, 14.2; IR (KBr) 3200 (OH), 2900, 1700 (C═O), 1560, 1440, 1400, 1260, 1200, 1060 cm^{-1}.

Methyl 2,3-dibromo-6-hexyl-5-hydroxybenzoate 17b (from 9b). R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 56 mg, 82% from ketone **9b**; solid, mp 70–72 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 3.93 (s, 3H, OMe), 2.44 (t, J = 8.0 Hz, 2H), 1.50–1.45 (m, 2H), 1.31–1.25 (m, 6H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 153.6, 138.2, 127.9, 122.5, 120.9, 111.6, 52.9, 31.4, 29.4 (2C), 28.5, 22.5, 14.0; IR (KBr) 3200 (OH), 2900, 1700 (C═O), 1560, 1440, 1400, 1260, 1200, 1060 cm^{-1}; HRMS (EI) Calcd for $C_{14}H_{18}Br_2O_3$ $[M]^+$, 391.9622; Found, 391.9605.

Methyl 2,3-dibromo-6-hexyl-5-hydroxybenzoate 17b (from 10b). R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 67 mg, 92% from ketone **10b**; solid, mp 70–72 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 3.93 (s, 3H, OMe), 2.43 (t, J = 8.0 Hz, 2H), 1.50–1.45 (m, 2H), 1.31–1.25 (m, 6H), 0.85 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 153.6, 138.2, 127.9, 122.5, 120.9, 111.6, 52.9, 31.4, 29.4 (2C), 28.5, 22.5, 14.0; IR (KBr) 3200 (OH), 2900, 1700 (C═O), 1560, 1440, 1400, 1260, 1200, 1060 cm^{-1}; Anal. Calcd for $C_{14}H_{18}Br_2O_3$: C, 42.67; H, 4.60. Found: C, 42.66; H, 4.58.

Methyl 3,4-dibromo-6-hydroxybiphenyl-2-carboxylate 17c (from 9c). R_f = 0.4 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 23 mg, 48% (for two steps) from the hydroxy compound **15c**; solid, mp 134–136 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.35 (m, 3H), 7.29–7.19 (m, 3H), 3.50 (s, 3H, OMe); IR (KBr) 3200 (OH), 2900, 1700 (C═O), 1560, 1440, 1400, 1260, 1200, 1060 cm^{-1}; Anal. Calcd for $C_{14}H_{10}Br_2O_3$: C, 43.56; H, 2.61. Found: C, 43.43; H, 2.79; HRMS (EI) Calcd for $C_{14}H_{10}Br_2O_3$ $[M]^+$, 383.8997; Found, 383.8995.

Methyl 3,4-dibromo-6-hydroxybiphenyl-2-carboxylate 17c (from 10c). R_f = 0.4 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 58 mg, 80% from **10c**; solid, mp 134–136 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.35 (m, 3H), 7.29–7.23 (m, 3H), 3.50 (s, 3H, OMe); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 152.6, 138.1, 132.1, 129.7 (2C), 129.6 (2C), 129.5, 126.7, 125.5, 121.5, 112.0, 52.7; IR (KBr) 3200 (OH), 2900, 1700 (C═O), 1560, 1440, 1400, 1260, 1200, 1060 cm^{-1}; Anal. Calcd for $C_{14}H_{10}Br_2O_3$: C, 43.56; H, 2.61. Found: C, 44.03; H, 2.67.

Methyl 2-butyl-5,6-dichloro-3-hydroxybenzoate 17d (from 9d). R_f = 0.5 [7% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 21 mg, 59% (for two steps) from the hydroxy compound **15d**; solid, mp 64–66 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 3.95 (s, 3H, OMe), 2.46 (t, J = 8.0 Hz, 2H), 1.52–1.46 (m, 2H), 1.37–1.31 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 152.9, 135.9, 130.5, 127.1, 120.1, 117.8, 52.8, 31.6, 27.9, 22.7, 13.8; IR (KBr) 3200 (OH), 2900, 1700 (C═O), 1560, 1440, 1400, 1260, 1200, 1060 cm^{-1}; Anal. Calcd for $C_{12}H_{14}Cl_2O_3$: C, 52.00; H, 5.09. Found: C, 51.86; H, 5.10.

Methyl 2-butyl-5,6-dichloro-3-hydroxybenzoate 17d (from 10d). R_f = 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_f = 0.8 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 298 mg, 60% from **11a** (based on the recovery of 18% unreacted **11a**); viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (d, J = 8.1 Hz, 1H, 2-H_{exo}), 5.52 (d, J = 7.8 Hz, 1H, 2-H_{exo}), 3.46 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.37 (s, 3H, OMe), 3.33 (s, 3H, OMe), 2.82–2.76 (m, 1H, 3-H_{exo}), 2.71–2.67 (m, 1H, 3-H_{exo}), 2.08 (s, 3H, $OCOCH_3$), 2.04 (s, 3H, $OCOCH_3$), 1.60–1.57 (m, 1H + 1H), 1.43–1.08 (m, 3H + 3H), 0.93–0.88 (m, 3H + 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 170.5, 126.4, 124.1, 120.6, 117.5, 113.1, 112.8, 79.3, 75.3, 73.2, 56.1–55.2 (m, 2C attached to D at C-1 and C-4), 52.9, 52.4, 50.7, 50.5, 50.1, 43.1, 27.7, 26.4, 21.9, 20.9, 20.7, 20.5, 14.2, 14.0; IR (neat) 2900, 1720 (C═O), 1600, 1440, 1360, 1220, 1020 cm^{-1}; Anal. Calcd for $C_{14}H_{18}DBr_3O_4$: C, 34.18; H, 4.10. Found: C, 34.44; H, 3.84; HRMS (ESI) Calcd for $C_{14}H_{18}DBr_3O_4Na$ $[M + Na]^+$, 511.8794; Found, 511.8796.

1,5,6-Tribromo-4-deutero-7,7-dimethoxy-3-propylbicyclo-[2.2.1]hept-5-en-2-ol 24. R_f = 0.6 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 58 mg, 29% from the mixture of **21** and **22**; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (d, J = 7.8 Hz, 1H, 2-H_{exo}), 3.40 (s, 3H, OMe), 3.38 (s, 3H, OMe), 2.65–2.59 (m, 1H, 3-H_{exo}), 1.67 (brs, 1H, OH), 1.47–1.16 (m, 4H), 0.94 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.3, 121.1, 112.9, 79.1, 76.9, 56.2–55.8 (m, C-4 attached to D), 52.4, 50.6, 43.2, 27.8, 21.6, 14.2; IR (neat): 3400 (OH), 2900, 1580, 1440, 1180 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{16}DBr_3O_3Na$ $[M + Na]^+$, 469.8688; Found, 469.8688.

4,5,6-Tribromo-1-deutero-7,7-dimethoxy-3-propylbicyclo-[2.2.1]hept-5-en-2-ol 25. R_f = 0.4 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 122 mg, 61% from the mixture of **21** and **22**; solid, mp 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (d, J = 7.6 Hz, 1H, 2-H_{exo}), 3.45 (s, 3H, OMe), 3.33 (s, 3H, OMe), 2.58–2.53 (m, 1H, 3-H_{exo}), 1.62–1.45 (m, 3H, OH peak buried under the peaks of 2H of the alkyl chain), 1.39–1.30 (m, 1H), 1.27–1.18 (m, 1H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.1, 117.4, 113.4, 75.9, 72.4, 58.7–58.1 (m, C-1 attached to D), 53.0, 51.1, 50.6, 26.1, 22.6, 14.4; IR (KBr) 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm^{-1}; Anal. Calcd for $C_{12}H_{16}DBr_3O_3$: C, 32.03; H, 4.03. Found: C, 32.46; H, 3.81.

1,5,6-Tribromo-4-deutero-7,7-dimethoxy-3-propylbicyclo-[2.2.1]hept-5-en-2-one 19. R_f = 0.7 [10% EtOAc in hexane (over 7% $AgNO_3$-impregnated silica gel)]; yield 47 mg, 86% from alcohol **24**; viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (s, 3H, OMe), 3.39 (s, 3H, OMe), 2.52 (dd, J = 4.3 Hz, 10.1 Hz, 1H, 3-H_{exo}), 1.74–1.68 (m, 1H), 1.47–1.34 (m, 2H), 1.26–1.19 (m, 1H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 126.3, 120.5, 115.8, 79.3, 55.6–55.0 (m, C-4 attached to D), 52.4, 50.9, 45.1, 30.7, 21.3, 13.7; IR (neat) 2900, 1740 (C═O), 1580, 1440, 1200, 1100, 960 cm^{-1}.

4,5,6-Tribromo-1-deutero-7,7-dimethoxy-3-propylbicyclo-[2.2.1]hept-5-en-2-one 20. R_f = 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, $CDCl_3$) δ 3.52 (s, 3H, OMe), 3.37 (s, 3H, OMe), 2.63 (dd, J = 5.2, 8.2 Hz, 1H, 3-H_{exo}), 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, $CDCl_3$) δ 202.7, 131.8, 115.9, 113.0, 71.9, 67.6–67.1 (m, C-1 attached to D), 53.5, 52.7, 51.0, 30.0, 21.7, 14.1; IR (neat) 2900, 1740 (C═O), 1600, 1440, 1200, 1100, 960 cm^{-1}; HRMS (ESI) Calcd for $C_{12}H_{14}DBr_3O_3$ $[M + H]^+$, 445.8712; Found, 445.8719.

Dibromophenol derivative 26 [18] from the fragmentation of ketone 19 using PTSA (Scheme 4). R_f = 0.6 [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, $CDCl_3$) δ 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, $CDCl_3$) δ 168.3, 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, 1400, 1260, 1200, 1060 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{13}Br_2O_3$ $[M + H]^+$, 350.9231; Found, 350.9231.

Dibromophenol derivative 27 [18] from the fragmentation of ketone 20 using PTSA (Scheme 4). R_f = 0.6 [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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, 1400, 1260, 1200, 1060 cm^{-1}; Anal. Calcd for $C_{11}H_{11}DBr_2O_3$: C, 37.42; H, 3.71. Found: C, 37.14; H, 3.37; HRMS (ESI) Calcd for $C_{11}H_{11}DBr_2O_3Na$ $[M + Na]^+$, 373.9114; Found, 373.9117.

Acknowledgements

F. A. K. gratefully acknowledges CSIR for financial support. S. C. and S. A. thank CSIR for fellowship.

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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.[5].

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