DOI: 10.1002/ejoc.201000071

An Efficient Synthesis of Substituted *meta*-Halophenols and Their Methyl Ethers: Insight into the Reaction Mechanism

Faiz Ahmed Khan*[a] and Sumit Choudhury[a]

Keywords: Oxidation / Ketones / Grob-type fragmentation / *meta*-Halophenols / Reaction mechanisms

An expeditious synthetic methodology leading to substituted *meta*-halophenols and their corresponding methyl ether derivatives through acid-mediated fragmentation of suitably substituted dihalonorbornyl ketones has been devised. The reaction sequence consists of TBTH-mediated (TBTH is tri-*n*-butyltin hydride) selective bridgehead halogen reduction of easily accessible Diels–Alder adducts derived from 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadiene and β-substituted vinyl acetates, with subsequent conversion into the requisite bicyclic ketones by a two-step hydrolysis/oxidation approach. An extensive mechanistic investigation based on isotope labeling and cross experiments has been carried out and plausible mechanistic pathways based on these results have been proposed. The absence of halogen atoms at the bridgehead positions steers the reaction through a novel pathway involving the incorporation of proton (or deuterium) followed by elimination of HX (or DX), so the described methodology also provides a reliable route to *ortho-para* dideuterated phenolic derivatives.

Introduction

Halophenols are ubiquitous because of their widespread occurrence in compounds ranging from naturally occurring bioactive molecules[1] to industrially important pharmaceuticals,[2] and serve as synthetic building blocks for the construction of these valuable entities. Chlorophenols are industrially important because of their broad spectrum of antimicrobial properties and their usage as fungicides, herbicides, insecticides, ovicides, and algicides.[2a] They are of further industrial significance as a result of their extensive usage as preservatives for wood, glue, paint, vegetable fibers, and leather.[2a,2b] On the other hand, differently substituted bromophenols have been found to exhibit a variety of bioactivities including enzyme inhibitory activities,[3] antibacterial activity,[4] cytotoxic activity,[5] and free radical scavenging activity.[6] Moreover naturally occurring volatile bromophenols have been found to be widely distributed in marine fish and seafood and have been recognized as important contributors to their flavors.[7] Recent studies have revealed wide occurrence of bromophenols in marine algae and this is believed to be a possible source of such compounds in fish that feed predominantly on ocean plants.[8] Interestingly a number of brominated phenols have been detected in the blood of humans, fish, and wild animals, and their role in living systems has been the subject of intense study.[9]

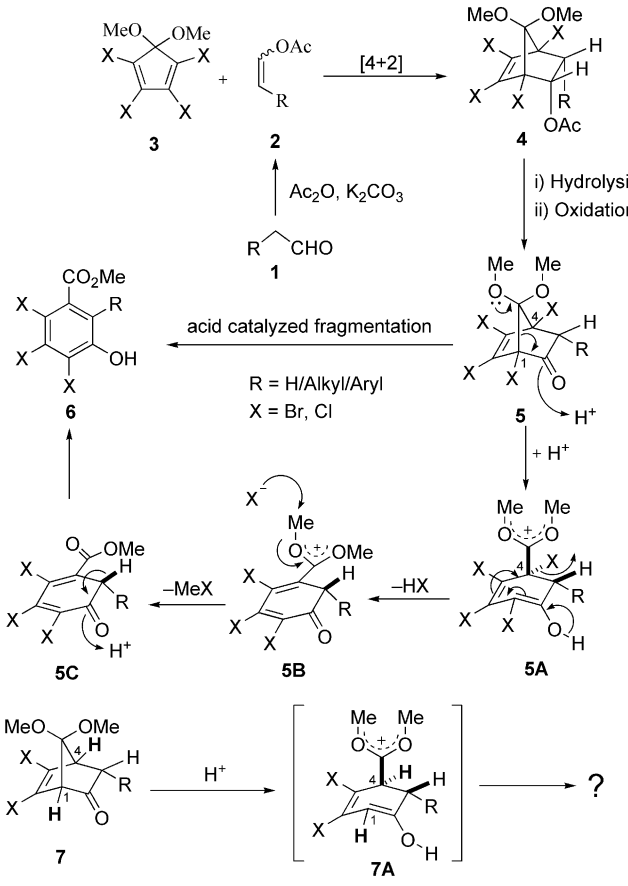
The enormous synthetic importance of substituted phenolic derivatives,[10] together with their biological properties, make them attractive targets, resulting in a plethora of synthetic endeavors. Halophenols are commonly synthesized through electrophilic aromatic halogenation reactions with employment of a variety of halogenating agents.[11] So far, a large number of methods for the synthesis of phenol derivatives have been reported.[12] Substituted phenols are conventionally prepared from benzenoid precursors,[12a–12f] acyclic precursors,[12g–12k] or non-benzenoid cyclic systems.[12l,12m] Straightforward routes to substituted *meta*-halophenols are scarce, however, because these are not accessible through conventional aromatic electrophilic substitution reactions, by virtue of the *ortho-para*-directing electronic effects of hydroxy (or alkoxy) groups, which determine the regioselectivity in aromatic substitution chemistry. Traditional approaches to these molecules involve the hydrolysis of diazonium salts, necessitating multistep reaction sequences including aromatic electrophilic substitution, which generally gives more than one regioisomer, thereby necessitating a rigorous purification process before proceeding further. Other than this traditional way, only two reports of the synthesis of substituted *meta*-halophenols are so far known. Patterson previously reported the synthesis of highly substituted *meta*-chlorophenols through Alder–Rickert reactions from starting chlorocyclohexa-1,3-diene derivatives.[13] Subsequently, Maleczka et al. developed an iridium-catalyzed method for synthesizing *meta*-halophenols bearing *ortho*/*para*-directing groups.[14]

As a consequence of our ongoing interest in applications of the norbornyl moiety as a versatile building block,[15] we had earlier reported an efficient synthesis of the trihalo-

[a] Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India
Fax: +91-512-2597436
E-mail: faiz@iitk.ac.in

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201000071.

phenol derivatives **6** (Scheme 1) from inexpensive and easily accessible starting materials such as the 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadienes **3** and the β-substituted vinyl acetates **2**, derived from aldehydes **1**.[16] Diels–Alder reactions between **2** and **3** furnished the cycloadducts **4**, which upon hydrolysis and subsequent oxidation of the resulting secondary alcohols gave the bicyclic ketones **5**.[16] Extending this concept, we have now achieved an easy route to substituted *meta*-halophenols and their methyl ethers, which are difficult to prepare by conventional routes. Here we wish to report an expeditious and flexible synthetic methodology leading to the title compounds. A detailed discussion of plausible reaction mechanisms with supporting evidence based on cross experiments and isotope labeling experiments is also presented.



Scheme 1. Synthesis and acid-catalyzed fragmentation of compounds **5**.

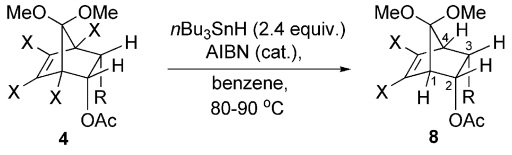
Results and Discussion

We had earlier proposed a mechanism involving acid-catalyzed Grob-type fragmentation of compounds **5** to afford the dienols **5A**.[16] The intermediates **5A** represent ideal push-pull systems because X at C^4, being a good leaving group, is present in conjugation with the dienol moiety. This is suitably positioned for HX elimination with simultaneous reorganization of double bonds to give the intermediates **5B**, which finally collapse to afford the trihalophenols **6** through enolization of **5C** (Scheme 1).[16]

In an attempt to extend and exploit this methodology, we wanted to examine the consequences of replacement of the bridgehead halogens in compounds **5** by hydrogen atoms and exposure of the resulting ketones **7** (Scheme 1) to similar acid treatment. We anticipated that the ketones **7** should undergo facile Grob-type fragmentations. However, because of the lack of a leaving group X at C^4, elimination of HX as shown in Scheme 1 for compounds **5** (**5A**) is not possible for compounds **7**, so a completely different mechanistic course for the initially formed fragmentation intermediates **7A** was expected.

With this objective, we first reduced the bridgehead halogens in the Diels–Alder adducts **4**, which had been prepared by our previously reported method (Scheme 1).[16] Regioselective bridgehead halogen reductions of compounds **4** were carried out with TBTH at reflux in benzene[17] to furnish compounds **8** in 72–80% yields (Table 1), except in the case of **8f**, for which the yield was 60%. The relatively unreactive chloro analogues required 50–60 hours for the completion of reaction to furnish the reduced products in good yields. The appearance of two doublets of doublets (dd) in ^{1}H NMR spectra of **8** in the δ = 3.0–3.5 ppm range indicated the replacement of halogens by hydrogen atoms at the bridgehead positions. The observed dds for the bridgehead protons H^1 and H^4 in the ^{1}H NMR spectra of **8** are due to their coupling with the corresponding vicinal *exo* protons H^2 and H^3, respectively, as well as "W" coupling with one another, which falls in the 2.2–2.4 Hz range (see Figure S1 in the Supporting Information). The appearance of a dd in the δ = 5.3–5.7 ppm range for *exo*-H^2 also

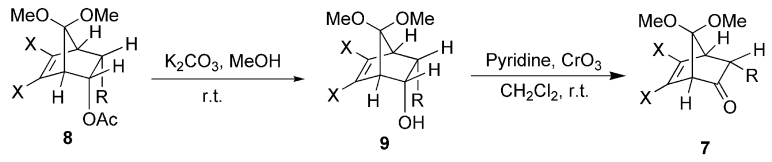
Table 1. TBTH-mediated reductions of the bridgehead halogens of compounds **4**.[a]



Entry	Substrate **4**	X	R	Time [h]	Product	Yield [%][b]
1	**4a**	Br	*n*-C_3H_7	2.5	**8a**	75
2	**4b**	Br	*n*-C_4H_9	3.5	**8b**	73
3	**4c**	Br	*n*-C_5H_{11}	2.5	**8c**	74
4	**4d**	Br	*n*-C_6H_{13}	3	**8d**	72
5	**4e**	Br	Ph	2.5	**8e**	80
6	**4f**	Br	H	1	**8f**	60
7	**4g**	Cl	*n*-C_3H_7	50	**8g**	80
8	**4h**	Cl	*n*-C_4H_9	60	**8h**	72
9	**4i**	Cl	*n*-C_5H_{11}	60	**8i**	77
10	**4j**	Cl	*n*-C_6H_{13}	60	**8j**	74
11	**4k**	Cl	Ph	60	**8k**	78

[a] The reactions were carried out in dry benzene (10 mL) with **4** (1 mmol), TBTH[c] (2.4 mmol), and AIBN (0.05 mmol) at reflux temperature (80–90 °C). [b] Isolated yield after column chromatography. [c] TBTH was distilled prior to use and purity was checked by GC analysis (ca. 95% purity).

Table 2. Hydrolysis of acetates **8** to alcohols **9**[a] and their oxidation to the corresponding ketones **7**.[b]



Entry	Substrate **8**	X	R	Alcohol **9**/time [h]/yield [%][c]	Ketone **7**/time [h]/yield [%][c]
1	**8a**	Br	*n*-C_3H_7	**9a**/20/91	**7a**/40/90
2	**8b**	Br	*n*-C_4H_9	**9b**/20/91	**7b**/40/91
3	**8c**	Br	*n*-C_5H_{11}	**9c**/25/95	**7c**/30/91
4	**8d**	Br	*n*-C_6H_{13}	**9d**/20/93	**7d**/40/90
5	**8e**	Br	Ph	**9e**/30/99	**7e**/30/92
6	**8f**	Br	H	**9f**/20/90	**7f**/40/90
7	**8g**	Cl	*n*-C_3H_7	**9g**/30/90	**7g**/30/91
8	**8h**	Cl	*n*-C_4H_9	**9h**/50/91	**7h**/40/90
9	**8i**	Cl	*n*-C_5H_{11}	**9i**/40/92	**7i**/50/92
10	**8j**	Cl	*n*-C_6H_{13}	**9j**/40/92	**7j**/40/94
11	**8k**	Cl	Ph	**9k**/50/90	**7k**/40/91

[a] Reactions were carried out in methanol (5 mL) with **8** (1 mmol) and K_2CO_3 (1.1 mmol) at room temperature. [b] Reactions were carried out in dichloromethane (50 mL) with **9** (1 mmol), anhydrous pyridine (13.3 mmol), and CrO_3 (6.6 mmol) at room temperature. [c] Isolated yield after column chromatography.

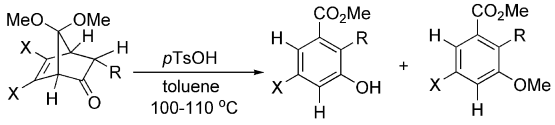
supports the above conjecture, because it also experiences vicinal couplings with *exo*-H^3 and H^1.

The acetates **8** were then hydrolyzed (K_2CO_3 in MeOH) to furnish the corresponding alcohols **9** in good to excellent yields (Table 2). Subsequently they were oxidized (Py/CrO_3 in dichloromethane) with in situ formation of pyridinium dichromate (PDC) to afford the corresponding bicyclic ketones **7** in high yields (Table 2).

The bicyclic ketones **7** were then treated with *p*TsOH (PTSA) in toluene at reflux. Unlike in the fragmentation of the tetrahalo analogues **5**, which had furnished the substituted trihalophenol derivatives **6** (Scheme 1),[16] two products were formed in this case. From their ^1H and ^{13}C NMR spectra, the structures of the two products were assigned as the substituted *meta*-halophenols **10** and the corresponding methyl ethers **11**, the former products being the major ones in all cases (Table 3). It is rather surprising to note that products with identical substitution patterns and each containing only one halogen atom were obtained. Unlike in the case of compounds **5**, neither of the two halogens present in the starting ketones **7** is suitably positioned for HX elimination, which means that a halogen atom X is lost from a position not well suited for elimination. At this stage, there were two issues to be settled: i) the mechanism of HX elimination, and ii) the origin of the methyl ether formation.

The NMR spectra of the compounds **10** and **11** showed similarities, but with compounds **11** each showing one extra peak (as a singlet) in the δ = 3.5–3.9 ppm range (corresponding to three protons) in the ^1H spectrum and in the δ = 52–57 ppm range in the ^{13}C NMR spectrum. The appearance in each case of two signals (both as doublets) in the aromatic region in the ^1H NMR spectra indicated that compounds **10** were monohalophenols (tetrasubstituted benzenes). To ascertain the substitution patterns of the aromatic moieties, analysis of the coupling constants of the aromatic protons was now carried out. Because they appeared as doublets with coupling constants ranging from 2–2.2 Hz, a typical value for *meta*-coupling, the products were assigned the structures **10**. Final confirmation of the structures was provided by acid-catalyzed fragmentation of **7f**. In its ^1H NMR spectrum the thus obtained phenol derivative **10f** showed three doublets in the aromatic region with *J* values typical for *meta*-coupling. This is possible only if three protons remain at the 1, 3, and 5 positions of the aromatic ring. Any other distribution would result in at least two hydrogen atoms *ortho* to each other with a characteristic *J* value in the 7–10 Hz range in the ^1H NMR spectrum of **10f**, and no such a feature is present.

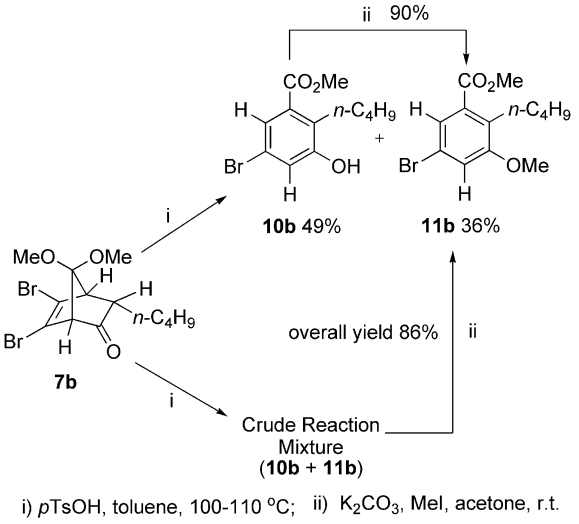
Table 3. Acid-catalyzed fragmentation of **7**.[a]



Entry	Substrate **7**	X	R	Time [h]	Product	Yield [%][b]
1	**7a**	Br	*n*-C_3H_7	10	**10a**, **11a**	60, 30
2	**7b**	Br	*n*-C_4H_9	10	**10b**, **11b**	49, 36
3	**7c**	Br	*n*-C_5H_{11}	8	**10c**, **11c**	53, 37
4	**7d**	Br	*n*-C_6H_{13}	8	**10d**, **11d**	56, 32
5	**7e**	Br	Ph	12	**10e**, **11e**	51, 32
6	**7f**	Br	H	1	**10f**, **11f**	42, 16
7	**7g**	Cl	*n*-C_3H_7	40	**10g**, **11g**	48, 35
8	**7h**	Cl	*n*-C_4H_9	30	**10h**, **11h**	44, 37
9	**7i**	Cl	*n*-C_5H_{11}	30	**10i**, **11i**	41, 39
10	**7j**	Cl	*n*-C_6H_{13}	30	**10j**, **11j**	45, 38
11	**7k**	Cl	Ph	30	**10k**, **11k**	44, 39

[a] The reactions were carried out in dry toluene (3 mL) with **7** (0.07 M, 0.21 mmol) and PTSA (0.21 mmol) at reflux temperature (100–110 °C). [b] Isolated yield after column chromatography.

Similar spectral analysis confirmed the structures of the other compounds **11** as the corresponding methyl ethers. The phenolic compound **10b**, isolated after treatment of **7b** with PTSA, gave **11b** on methylation with MeI/K_2CO_3 (Scheme 2). When the crude reaction mixture obtained from the same reaction (containing both **10b** and **11b** as indicated by TLC) was treated with MeI/K_2CO_3 in acetone, exclusive formation of **11b** was achieved, which unequivocally confirmed the structure of **11b** as the methyl ether derivative of **10b**.

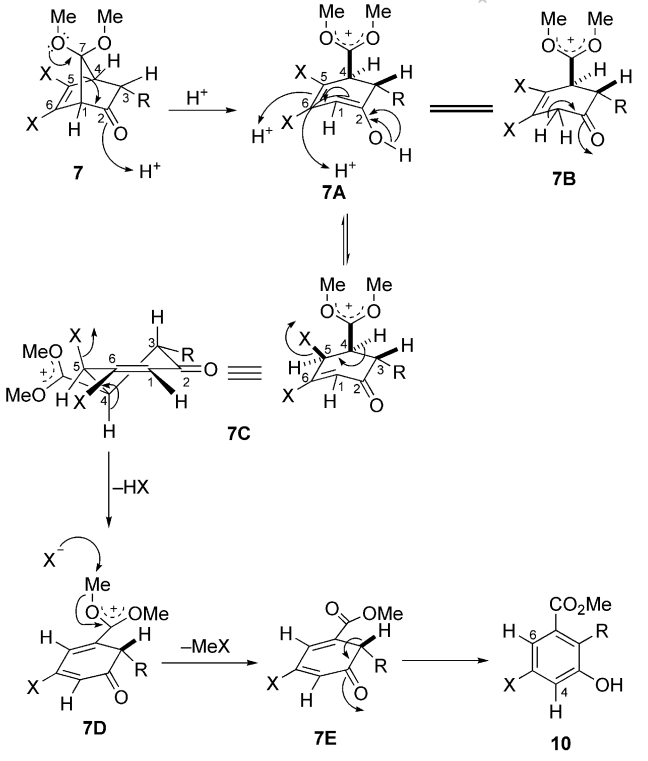


Scheme 2. Structural confirmation of the formation of methyl ethers of the *meta*-halophenols **10**.

Substituted *meta*-halophenols are valuable intermediates in organic synthesis, having been found to be useful both in materials science[18] and in the pharmaceutical industry.[19] Müller et al. utilized the ethyl ester analogue of **10f** as a functionalized building block for the construction of multifunctional molecular materials such as preorganized oligofunctional amphiphiles[18] and a thrombin inhibitor was successfully synthesized by Lu et al. through employment of the benzyl ester derivative of the chloro analogue of **10f**.[19]

Having confirmed the structures of **10** and **11**, our next task was to propose a mechanism to explain the product formation. A plausible mechanism based on our previous work[16] and the above experimental results is depicted in Scheme 3. On exposure to acid, protonation at the carbonyl group of **7**, followed by cleavage of the C^1–C^7 sigma bond in a Grob fragmentation pattern in a similar manner as observed with **5** (Scheme 1), results in the formation of the resonance-stabilized intermediate oxocarbenium ion **7A** (for convenience, the same numbering sequence as for **7** is retained for other intermediates).

In the case of cleavage of compounds **5**, C^4 was substituted at this stage with halogen (X, **5A**, Scheme 1). Its subsequent removal from the system as X^- facilitated the generation of an intermediate **5B** capable of triggering extrusion of gaseous MeX. Because a hydrogen atom is present at C^4

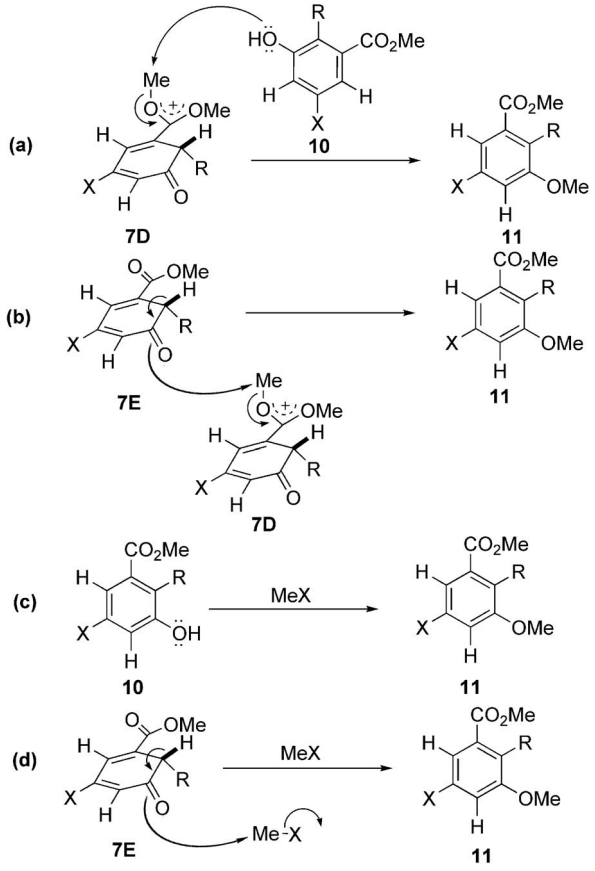


Scheme 3. Plausible mechanism for fragmentation of compounds **7**.

in the current case, the earlier mechanism is ruled out, thus necessitating the postulation of a different route. The intermediates **7A**, each containing a dienol moiety as represented by C^5–C^6–C^1–C^2–OH, could undergo protonation by external acid either at the β-carbon (i.e., C^1) or at the δ-carbon (i.e., C^5) of the dienol moiety from the less hindered face [opposite to bulky $C(OMe)_2^+$ group] as shown in Scheme 3. Protonation at the β-carbon would generate intermediates **7B**, which could revert back to the original **7A** through enolization. On the other hand, protonation at the δ-carbon would result in the formation of intermediates **7C**. These, being cyclohexenone derivatives, can be represented in a half-chair conformation in which H^4 and X^5 occupy axial and pseudoaxial positions, respectively. As a result, the acidic proton H^4 and halogen X^5 could then undergo facile 1,2-elimination to form **7D**. The halide X^- could then nucleophilically attack the oxocarbenium ions **7D** at the methyl carbon to form gaseous MeX and cyclohexadienone moieties **7E**. Finally, the substituted *meta*-halophenols **10** could be obtained through enolization of intermediates **7E** (Scheme 3).

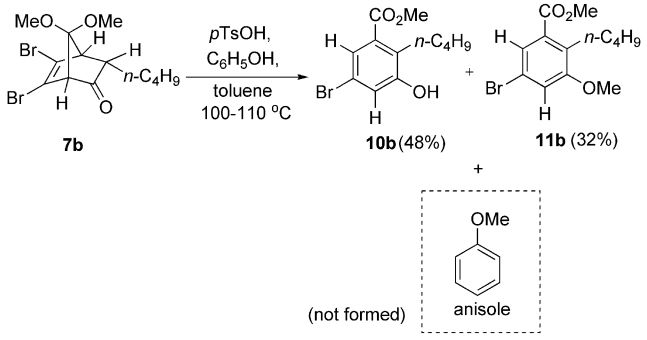
Although this mechanism would suffice to explain the formation of the phenols **10** from the cyclohexadienones **7E**, further pathways are required in order to explain the formation of the corresponding methyl ether derivatives **11**.[20] The fundamental question is: which species is acting as the methylating agent? In principle, the oxocarbenium species **7D** and/or the MeX generated during the reaction could be responsible for methylation, whereas the nucleophilic species that undergo methylation could be either the

phenol derivatives **10** or the intermediate cyclohexadienones **7E**. Keeping this in mind, four hypotheses may be envisaged, as shown in Scheme 4.



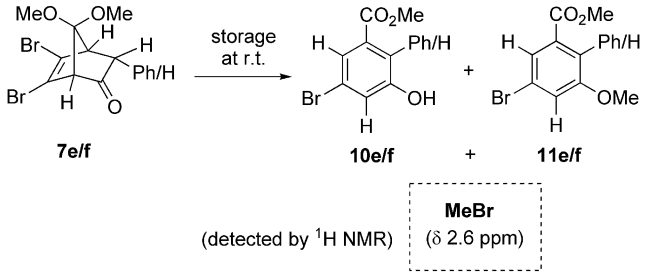
Scheme 4. Possible routes for the formation of **11**.

If route (a) depicted in Scheme 4 is operative, then addition of phenol (C_6H_5OH) to the reaction mixture should furnish anisole (C_6H_5OMe) as one of the products, due to competition of added phenol with **10**. To address this issue, a known quantity of phenol was added to the reaction mixture during the fragmentation reaction of **7b** (R = *n*-C_4H_9) in the presence of PTSA in toluene at reflux (Scheme 5). Interestingly, we did not observe any change in the outcome of the reaction, with only the normal products (i.e., the phenol derivative **10b** and its methyl ether **11b**) being formed; no anisole formation was detected (as indicated by GC analysis). Consequently, a mechanism of this type can probably be ruled out.



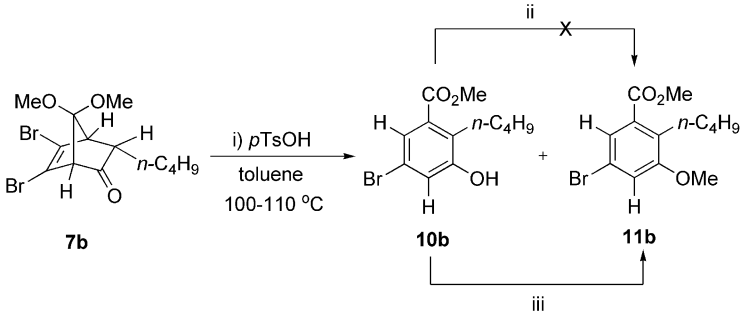
Scheme 5. Fragmentation reaction of **7b** in the presence of phenol.

Route (b) (Scheme 4) is incompatible with the in situ generation of gaseous MeX, the evolution of which during the course of reaction had been unequivocally corroborated spectroscopically by the appearance of sharp singlets at δ = 2.6 ppm (characteristic of MeBr) in the ^{1}H NMR spectra of the crude products obtained from the decomposition either of **7e** or of **7f** (Scheme 6).[21]



Scheme 6. Decomposition of **7e/7f** at room temperature.

To test the feasibility of route (c) as shown in Scheme 4, methylation of **10b** with MeI was attempted under conditions similar to those of the fragmentation reaction (Scheme 7). When the phenol derivative **10b** was subjected



ii) MeI, toluene, reflux: no reaction; then addition of PTSA, reflux: no reaction.

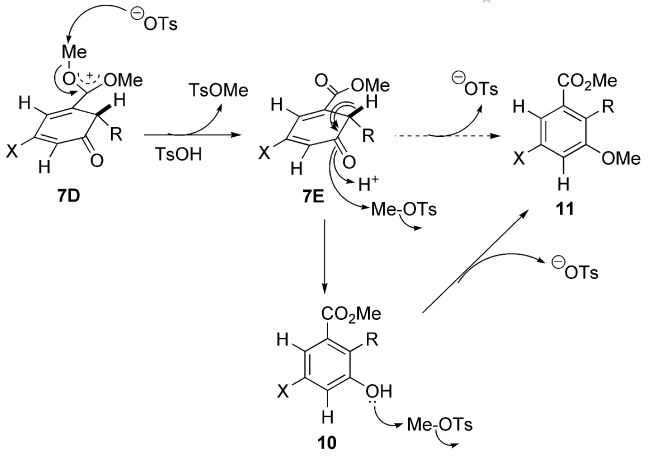
iii) acetone, MeI, r.t.: no reaction; then addition of K_2CO_3, stirring at r.t.: reaction completed, 90% yield of **11b**.

Scheme 7. Attempted methylation of **10b** under different conditions.

to treatment with MeI in toluene in the absence of any base, no reaction took place either at room temperature or at elevated temperature. As expected, addition of PTSA to the reaction mixture was unable to change the course of the reaction, whereas the reaction took place only when K_2CO_3 was added (Scheme 7). Because there is no possibility of any basic species being generated during the acid-catalyzed fragmentation reaction in toluene at reflux, route (c) in Scheme 4 can also be eliminated.

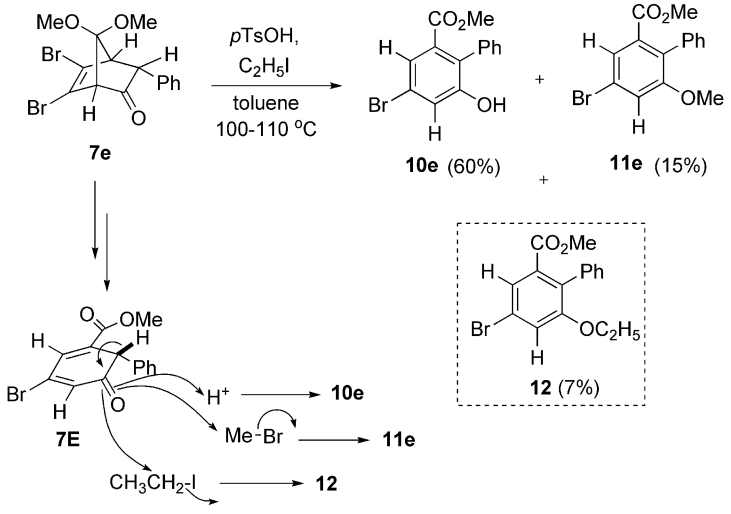
Route (d) in Scheme 4 thus appears to be the most likely pathway for the formation of **11**. In order to obtain evidence in support of this, the fragmentation reaction was carried out with the ketone **7e** (R = Ph) under optimized conditions with the additional presence of a different electrophile, ethyl iodide, in excess (Scheme 8).[22] It was observed that in addition to the normal products **10e** and **11e**, some quantities of the corresponding ethyl ether **12** were also formed (Scheme 8). This indicates that the cyclohexadienone moiety **7E** acts as a nucleophilic species and that H^+, MeBr (generated during the reaction) and the added C_2H_5I compete as electrophiles. As would be expected on the basis of the steric requirements of the competing electrophiles (H^+/MeBr/C_2H_5I), H^+ would win the race to furnish **10e** as the major product. Factors such as primary vs. secondary and bromo vs. iodo govern the balance between the electrophilic species MeBr and C_2H_5I, eventually leading to the minor products **11e** and **12** in approximately 2:1 ratio (isolated yields). This supports route (d) as depicted in Scheme 4.

At this point, if the availability of tosylate anion (TsO^-), produced from PTSA during the course of the reaction, is kept in mind, one might conceive that presence of PTSA plays a role in the formation of the methyl ether derivatives **11**, because TsO^- could attack the intermediate oxocarbenium ions **7D** at the methyl carbon thereby generating **7E** and TsOMe, which may act as a methylating agent[23] either during enolization of the species **7E** and/or through direct methylation of the phenols **10** already formed in the reaction, thus affording compounds **11** (Scheme 9).

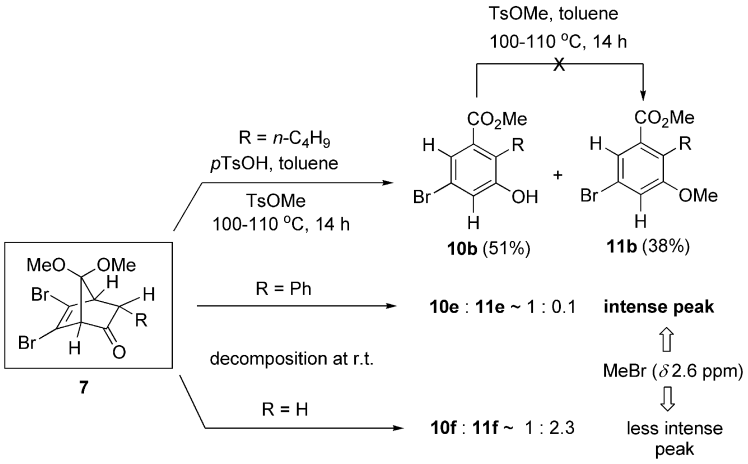


Scheme 9. Another possible route for the formation of compounds **11**.

To check this, **7b** was subjected to optimized conditions for the fragmentation reaction in the presence of TsOMe (Scheme 10). No significant change in the **10b/11b** ratio was noticed. Further, in a separate experiment, **10b** was also allowed to react with TsOMe in toluene at reflux. The methyl ether **11b** was not observed, thus ruling out the possibility of direct methylation of the phenols **10** by TsOMe (Scheme 10). Additional support in favor of route (d) was provided by the gradual decomposition of **7e** and **7f** on storage at room temperature (Scheme 6). ^{1}H NMR spectral analysis of the decomposed **7e** showed the presence of **10e** and **11e** in approximately 1:0.1 ratio whereas the same for **7f** showed **10f** and **11f** in a ratio of 1:2.3 along with MeBr in both cases (Scheme 10). However, the intensity of the peak at δ = 2.6 ppm in the ^{1}H NMR spectrum (characteristic of MeBr) is significantly smaller in the case of **7f** than in that of **7e** because the majority of the MeBr was used up as a result of nucleophilic attack during the enolization of intermediate cyclohexadienone to form the methyl ether derivative **11f** (see the Supporting Information).



Scheme 8. Fragmentation reaction of **7e** in the presence of ethyl iodide.

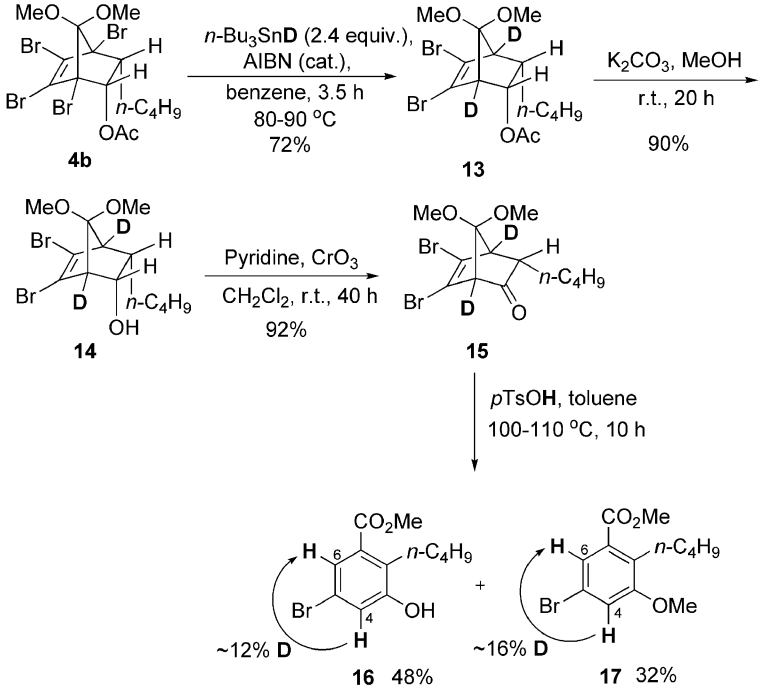


Scheme 10. Fragmentation of the bicyclic ketones **7** under different sets of conditions.

Now, to ascertain the fate of the bridgehead hydrogen atoms in the bicyclic ketones **7** during the proposed mechanistic course, the ideal solution would therefore be to replace them with deuterium and then to carry out the acid-mediated fragmentation reaction with a non-deuterated acid source. Alternatively, the bicyclic ketones **7** (non-deuterated at bridgehead positions) could be subjected to a deuterated acidic reagent. NMR and mass spectrometry could then be used to identify and locate hydrogen and/or deuterium present in the products, thus providing further insight into the mechanism.

In order to obtain such labeled bicyclic ketones, the bridgehead halogens of the initial acetate adducts **4** would need to be replaced by deuterium with subsequent execution of the known sequence of reactions. Compound **4b** was taken as a model substrate for this purpose and was reduced with tri-*n*-butyltin deuteride (TBTD),[24] prepared by reduction of tri-*n*-butyltin chloride (TBTCl) with lithium aluminium deuteride ($LiAlD_4$), to furnish the dideuterated compound **13** in 72% yield (Scheme 11).

Evidence for the replacement of the bridgehead halogens of **4b** by deuterium was obtained from NMR spectroscopic data. The absence of two peaks due to the bridgehead protons in the δ = 3–3.5 ppm range in ^{1}H NMR spectrum and the appearance of a doublet (d) for *exo*-2-H, instead of a doublet of doublets (dd) as observed in **8b**, confirmed the incorporation of deuterium at the bridgehead positions. Comparison of ^{13}C NMR spectra with **8b** also indicated the replacement of two intense peaks at δ = 57.9 and 57.7 ppm by weak peaks of multiplet nature arising from C–D cou-

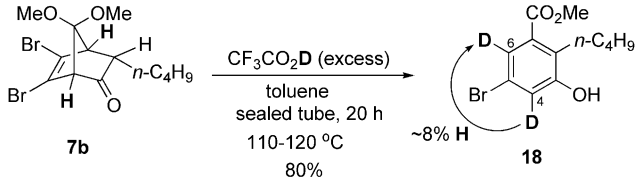


Scheme 11. Synthesis of **15** (with bridgehead deuterium) and its fragmentation reaction in the presence of protonated acid.

pling, which further confirmed the structure of **13** (see the Supporting Information). This was then converted into the bicyclic ketone **15** by a two-step hydrolysis/oxidation method in high yield. When the ketone **15** was treated with PTSA in toluene at reflux both the phenol **16** and its methyl ether **17** were formed in 48% and 32% yields, respectively.

Although PTSA had induced the fragmentation reaction, in order to know the exact roles of the bridgehead hydrogen atoms, it was also necessary to have some other acid, strong enough to cause the above reaction and with an easily available deuterated version. In this context, several acidic reagents were tested under varying reaction conditions with **7b** as model substrate (see Table S1 in the Supporting Information). It was observed that treatment of **7b** with excess trifluoroacetic acid (TFA) in a sealed tube at 110–120 °C resulted in the formation of only one product: the phenol derivative **10b**. No methyl ether **11b** was obtained, perhaps due to the presence of large amount of H^+.

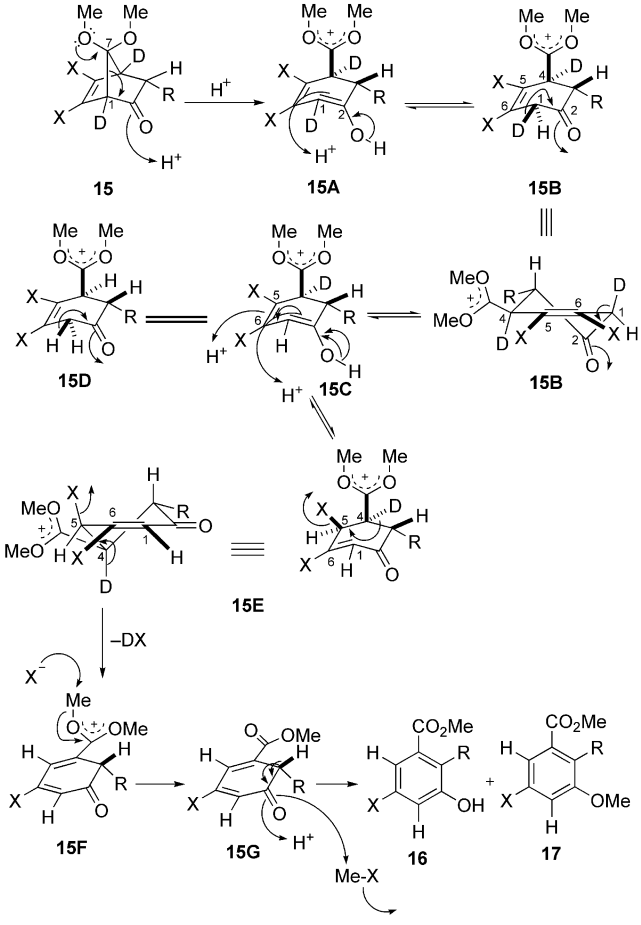
When the ketone **7b** (with hydrogen atoms at its bridgehead positions) was treated with excess CF_3COOD in toluene in a sealed tube at 110–120 °C only the phenol derivative **18** was formed (Scheme 12).



Scheme 12. Fragmentation reaction of **7b** (not deuterated at the bridgehead positions) in the presence of a deuterated acid.

To visualize the presence and extent of deuteration in the products obtained from these experiments, comparison of both ^1H and ^{13}C NMR spectra of products **16**, **18**, and the corresponding normal phenolic compound **10b** was now carried out (see Figure S2 and Figure S3 in the Supporting Information). Analysis of the integrals of different signals in the ^1H NMR spectrum of **16** in relation to that of **10b** revealed it to be mostly, but not exclusively, protonated, with the presence of ca. 12% deuterium (as calculated on the basis of integrals of different signals) being observed in **16**. Mass spectral analysis (see the Supporting Information) also supports the presence of minor quantities of deuterium in **16**. On the other hand, a ^1H and ^{13}C NMR spectral study of **18** found an almost reversed situation with regard to deuterium content, as observed in the form of ca. 92% deuterium incorporation in **18**, which was further supported by its mass spectrum. Similar ^1H NMR spectral analysis of **17** in relation to that of **11b** indicates ca. 16% deuterium occurrence.

In accordance with these results, the following mechanistic proposals have been made to interpret the observed proton/deuterium induction as shown in Scheme 13 and in Scheme 14 (below). In the cleavage of **15**, the intermediate oxocarbenium ion **15A** formed by protonation and subsequent C^1–C^7 sigma bond cleavage can undergo a series of deuterium/proton transfer steps to form **15C** (Scheme 13). During its formation, deuterium initially attached to C^1 is probably mostly exchanged for hydrogen from the external acidic reagent through the process of keto–enol tautomerism. It is presumed that, during this process, electrophilic attack at the C^1–C^2 double bond by the proton supplied by the acid takes place, predominantly from the less hindered face [opposite the bulky $C(OMe)_2^+$ group], forcing the existing deuterium at C^1 to the more hindered face to generate the cyclohexenone intermediate **15B** in which the deuterium at C^1 occupies a pseudoaxial position. Thus, during enolization, preferential involvement of pseudoaxially positioned deuterium, giving rise to **15C**, can be anticipated. Subsequent preferential protonation at the C^5–C^6 vinylic double bond from the less hindered bottom face by the acid to generate **15E**, 1,2-elimination of DX from this, followed by nucleophilic capture of the methyl group of the resulting **15F** by X^-, and final enolization of the consequent cyclohexadienone moiety **15G** leads to the formation of products **16** and **17**.

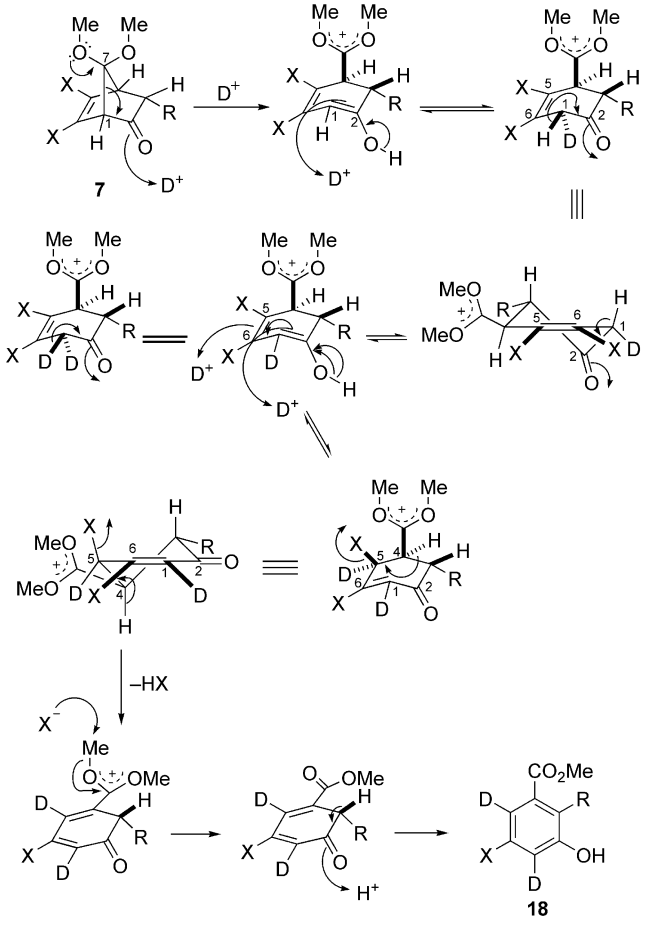


Scheme 13. Plausible mechanism in which the substrate is deuterated and the acidic reagent is not deuterated.

Of the two deuterium atoms present in **15**, the one at C^1 is lost during exchanges with H^+ supplied by the acidic reagent and the other at C^4 is removed as DX. On the other hand, electrophilic attack at the δ-carbon of the dienol moiety in **15C** (i.e., at C^5) is predominantly by H^+ of the acid used. As a result, the final phenol derivatives **16** and **17** are

found to be predominantly protonated at C^4 and C^6, as evidenced by the presence of only ca. 12% and ca. 16% deuterium in **16** and **17**, respectively. The reagent PTSA was used as its monohydrate form (pTsOH·H_2O) to effect the fragmentation reactions of the bicyclic ketones; the water molecule might thus be acting as an additional proton source. Minor deuteration can be explained on the basis of competitive participation by D^+ produced during the course of the reaction, which is of course outstripped by the already existing H^+ source.

On the other hand, the fragmentation reaction of **7b** in the presence of [D]TFA (CF_3COOD) can be mechanistically interpreted (Scheme 14) in a similar fashion, the only difference being hydrogen taking the place of deuterium and vice versa. In this case the presence of hydrogen (ca. 8%) at C^4 and C^6 of **18**, which is comparable with the previous result of ca. 12% deuterium occurrence at C^4 and C^6 of **16**, also supports the discussed mechanistic explanations. The D^+ was present in large excess in the latter case (1.5 mL for 0.1 mmol of **7b** i.e. ca. 200 equivalents), which was found to be an experimental requirement rather than a choice to induce the fragmentation reaction of **7b** (Scheme 12) as explained earlier. The large excess of D^+ was therefore assumed to have almost nullified the effectiveness of MeX generated in situ in acting as a competing electrophile, thus ruling out the formation of the methyl ether derivative.



Scheme 14. Plausible mechanism in which the substrate is not deuterated and the acid catalyst is deuterated.

Conclusions

In summary, we have developed an efficient route for the synthesis of substituted *meta*-halophenol derivatives and the corresponding methyl ether derivatives through acid-catalyzed fragmentation of dihalonorbornyl ketones. The overall transformations are based on a four-step protocol starting from easily accessible Diels–Alder adducts of 1,2,3,4-tetrahalo-5,5-dimethoxycyclopentadienes and β-substituted vinyl acetates. TBTH-mediated reduction of the bridgehead halogens of the initial adducts, followed by hydrolysis, oxidation of the resulting secondary alcohols, and finally acid-mediated fragmentation of the corresponding bicyclic ketones, led to the title compounds. Detailed mechanistic investigation involving isotope labeling and cross experiments was carried out, and plausible mechanistic pathways based on the results of these experiments and the products (or byproducts) formed, as well as on spectroscopic data, have been proposed. The experimental results clearly demonstrate that the external proton (or deuterium) supplied by the acidic reagent used is being incorporated predominantly in the final products. The formation of the methyl ether derivatives has been explained in terms of nucleophilic attack at the methyl halide generated in situ during the enolization of the cyclohexadienone moiety presumably produced as an intermediate during the course of the reaction. Although PTSA in stoichiometric quantities afforded both products, trifluoroacetic acid furnished only the phenolic derivatives, probably because of its usage in excess, which was found to be an experimental requirement rather than a matter of choice. The methodology also provides a reliable route to *ortho-para*-dideuterated phenolic derivatives.

Experimental Section

General Methods: All reactions were performed in oven-dried apparatus. All common reagents were obtained from commercial suppliers and were used without further purification. Commercial grade solvents were distilled by standard methods. Thin layer chromatography was performed on microscopic 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 ethanolic H_2SO_4 (4%) followed by charring. Column chromatography was performed with silica gel (100–200 mesh) and various combinations of ethyl acetate and hexane were used as eluents. $AgNO_3$-impregnated silica gel for column chromatography was prepared by mixing silica gel and $AgNO_3$ (7 wt.-%) in the minimum amount of water sufficient to generate a homogeneous slurry, followed by evaporation of water with heating and subsequent drying overnight in an oven. Melting points reported are uncorrected. IR spectra were recorded with Perkin–Elmer 1320 and Shimadzu 420 spectrophotometers as KBr pellets (solids) or thin films (liquids). ^1H NMR and proton-decoupled ^{13}C NMR spectra were recorded with a JEOL spectrophotometer at 400 and 100 MHz respectively. Sam-

ples for NMR were dissolved in $CDCl_3$. The chemical shifts (δ, ppm) and coupling constants J (Hz) are reported in the standard fashion with reference either to internal tetramethylsilane (for ^1H) or to the central line (δ = 77.0 ppm) of $CDCl_3$ (for ^{13}C). Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet. High-resolution mass spectra were recorded with a WATERS Q-TOF micro mass spectrometer in the electron spray ionization (ESI) mode and with a WATERS GCT micro mass spectrometer in the electron ionization (EI) mode. Elemental analyses were performed with a CE-440 Elemental Analyzer (Exeter Analytical Inc.).

General Procedure for Bridgehead Halogen Reduction of Tetrahalonorbornyl Acetates 4 to Generate Compounds 8

5,6-Dibromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-yl Acetate (8a): Tri-*n*-butyltin hydride (1.203 gm, 4.13 mmol) and azobis(isobutyronitrile) (AIBN) (13 mg, 0.08 mmol) were added under argon to a solution of **4a** (900 mg, 1.58 mmol) in dry benzene (15 mL). The reaction mixture was then heated at reflux under argon for 2.5 h until complete disappearance of starting material by TLC. The reaction mixture was then concentrated under reduced pressure to remove the solvent and the resulting crude mass was used for chromatographic separation. The tin impurities were first removed by adsorption of the oily crude mass over 7% $AgNO_3$-impregnated silica gel, followed by elution with EtOAc/hexane (5%). The resulting light yellow liquid was further purified by column chromatography over silica gel with prolonged hexane elution followed by a controlled increase of polarity with EtOAc/hexane solvent systems (up to 2% EtOAc/hexane as eluent) to furnish the doubly reduced product **8a**. R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 488 mg, 75%; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.40 (dd, J = 4.1, 7.8 Hz, 1 H, 2-H_{exo}), 3.41 (dd, J = 2.2, 4.2 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.08 (dd, J = 2.3, 3.3 Hz, 1 H, 4-H), 2.62–2.57 (m, 1 H, 3-H_{exo}), 2.01 (s, 3 H, $OCOCH_3$), 1.42–1.38 (m, 1 H), 1.28–1.16 (series of m, 3 H), 0.89 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 121.7, 118.6, 114.9, 73.5, 57.9, 57.6, 51.9, 49.7, 41.7, 28.3, 21.7, 20.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1580, 1440, 1360, 1220, 1020, 720 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{20}Br_2O_4$ $[M]^+$ 409.9728; found 409.9729.

5,6-Dibromo-3-butyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (8b): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 426 mg, 73% from **4b**, viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.39 (dd, J = 4.2, 7.8 Hz, 1 H, 2-H_{exo}), 3.42 (dd, J = 2.2, 3.9 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.08 (br. t, J = 2.3 Hz, 1 H, 4-H), 2.64–2.58 (m, 1 H, 3-H_{exo}), 2.01 (s, 3 H, $OCOCH_3$), 1.34–1.19 (series of m, 6 H), 0.88 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 121.7, 118.6, 114.9, 73.5, 57.9, 57.7, 51.9, 49.7, 41.9, 30.7, 25.8, 22.7, 20.8, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1740 (C=O), 1580, 1460, 1370, 1210, 1040 cm^{-1}. EI-HRMS: *m*/*z* calcd. for $C_{15}H_{22}Br_2O_4$ $[M]^+$ 423.9885; found 423.9883.

5,6-Dibromo-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-yl Acetate (8c): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 488 mg, 74% from **4c**, viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.39 (dd, J = 4.0, 7.7 Hz, 1 H, 2-H_{exo}), 3.41 (dd, J = 2.2, 4.2 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.09 (br. t, J = 2.8 Hz, 1 H, 4-H), 2.60–2.54 (m, 1 H, 3-H_{exo}), 2.01 (s, 3 H, $OCOCH_3$), 1.39–1.23 (series of m, 8 H), 0.87 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 121.7, 118.6, 114.9, 73.5, 57.9, 57.6, 51.9, 49.7, 42.0, 31.9, 28.2, 26.1, 22.5, 20.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1580, 1440, 1360, 1220, 1040, 720 cm^{-1}. $C_{16}H_{24}Br_2O_4$ (440.17): calcd. C 43.66, H 5.50; found C 43.83, H 5.35.

5,6-Dibromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (8d): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 438 mg, 72% from **4d**, viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.39 (dd, J = 4.2, 7.8 Hz, 1 H, 2-H_{exo}), 3.41 (dd, J = 2.3, 4.0 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.09 (br. t, J = 2.8 Hz, 1 H, 4-H), 2.60–2.53 (m, 1 H, 3-H_{exo}), 2.01 (s, 3 H, $OCOCH_3$), 1.39–1.17 (series of m, 10 H), 0.86 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 121.7, 118.6, 114.9, 73.5, 57.9, 57.7, 51.9, 49.7, 42.0, 31.7, 29.3, 28.5, 26.2, 22.6, 20.8, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1580, 1440, 1360, 1220, 1040, 720 cm^{-1}.

5,6-Dibromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-yl Acetate (8e): R_f = 0.6 [EtOAc/hexane 10% (over 7% $AgNO_3$-impregnated silica gel)]; yield 502 mg, 80% from **4e**; solid, m.p. 110–112 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.15 (m, 5 H, Ph), 5.68 (dd, J = 4.0, 7.7 Hz, 1 H, 2-H_{exo}), 3.88 (dd, J = 3.6, 7.7 Hz, 1 H, 3-H_{exo}), 3.53 (dd, J = 2.3, 4.0 Hz, 1 H, 1-H), 3.27 (s, 3 H, OMe), 3.22 (s, 3 H, OMe), 3.20 (dd, J = 2.3, 3.5 Hz, 1 H, 4-H), 2.01 (s, 3 H, $OCOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 135.3, 131.1 (2 C), 127.7 (2 C), 127.1, 123.3, 120.1, 115.2, 74.7, 61.0, 58.5, 52.1, 49.9, 48.3, 20.6 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1720 (C=O), 1580, 1480, 1440, 1360, 1220, 1080, 1040, 840, 760, 700 cm^{-1}. $C_{17}H_{18}Br_2O_4$ (446.13): calcd. C 45.77, H 4.07; found C 46.24, H 3.95.

5,6-Dichloro-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-yl Acetate (8g): R_f = 0.6 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 1.4 g, 80% from **4g**, viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.38 (dd, J = 4.0, 7.7 Hz, 1 H, 2-H_{exo}), 3.33 (dd, J = 2.4, 4.1 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.14 (s, 3 H, OMe), 3.01 (br. t, J = 2.8 Hz, 1 H, 4-H), 2.58–2.53 (m, 1 H, 3-H_{exo}), 1.99 (s, 3 H, $OCOCH_3$), 1.40–1.12 (m, 4 H), 0.88 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 128.7, 125.8, 114.2, 73.6, 56.2, 55.9, 51.8, 49.6, 41.6, 28.4, 21.5, 20.7, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1600, 1440, 1360, 1220, 1020, 720 cm^{-1}. $C_{14}H_{20}Cl_2O_4$ (323.22): calcd. C 52.02, H 6.24; found C 51.54, H 6.06.

3-Butyl-5,6-dichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (8h): R_f = 0.6 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 662 mg, 72% from **4h**, viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.39 (dd, J = 4.0, 7.7 Hz, 1 H, 2-H_{exo}), 3.34 (dd, J = 2.3, 4.0 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.02 (br. t, J = 2.9 Hz, 1 H, 4-H), 2.57–2.51 (m, 1 H, 3-H_{exo}), 2.00 (s, 3 H, $OCOCH_3$), 1.35–1.17 (series of m, 6 H), 0.87 ppm (t, J = 7.1 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 128.7, 125.8, 114.2, 73.5, 56.1, 55.9, 51.9, 49.6, 41.8, 30.5, 25.9, 22.7, 20.8, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1600, 1440, 1360, 1220, 1020, 720 cm^{-1}. $C_{15}H_{22}Cl_2O_4$ (337.24): calcd. C 53.42, H 6.58; found C 53.32, H 6.35.

5,6-Dichloro-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-yl Acetate (8i): R_f = 0.6 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 1.05 g, 77% from **4i**, viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.39 (dd, J = 4.1, 7.8 Hz, 1 H, 2-H_{exo}), 3.34 (dd, J = 2.4, 3.9 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.02 (br. t, J = 2.8 Hz, 1 H, 4-H), 2.56–2.52 (m, 1 H, 3-H_{exo}), 2.00 (s, 3 H, $OCOCH_3$), 1.36–1.14 (series of m, 8 H), 0.86 (t, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 128.7, 125.8, 114.2, 73.5, 56.2, 55.9, 51.8, 49.6, 41.9, 31.9, 28.0, 26.2, 22.5, 20.7, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1600, 1440, 1360, 1240, 1040, 720 cm^{-1}. $C_{16}H_{24}Cl_2O_4$ (351.27): calcd. C 54.71, H 6.89; found C 54.71, H 6.74.

5,6-Dichloro-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (8j): R_f = 0.6 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 580 mg, 74% from **4j**, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.39 (dd, J = 4.2, 7.8 Hz, 1 H, 2-H_{exo}), 3.34 (dd, J = 2.3, 4.0 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 3.02 (dd, J = 2.4, 3.4 Hz, 1 H, 4-H), 2.55–2.52 (m, 1 H, 3-H_{exo}), 2.00 (s, 3 H, $OCOCH_3$), 1.35–1.16 (series of m, 10 H), 0.86 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 128.7, 125.8, 114.2, 73.5, 56.2, 55.9, 51.8, 49.6, 41.9, 31.7, 29.3, 28.3, 26.3, 22.6, 20.7, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720, 1600, 1440, 1360, 1220, 1040, 720 cm^{-1}. HRMS (ESI): *m*/*z*: calcd. for $C_{17}H_{27}Cl_2O_4$ $[M + H]^+$ 365.1286; found 365.1284.

5,6-Dichloro-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-yl Acetate (8k): R_f = 0.7 [EtOAc/hexane 10% (over 7% $AgNO_3$-impregnated silica gel)]; yield 262 mg, 78% from **4k**, viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 3 H), 7.17–7.14 (m, 2 H), 5.68 (dd, J = 3.9, 7.8 Hz, 1 H, 2-H_{exo}), 3.88 (dd, J = 3.4, 7.6 Hz, 1 H, 3-H_{exo}), 3.46 (dd, J = 2.4, 4.2 Hz, 1 H, 1-H), 3.27 (s, 3 H, OMe), 3.24 (s, 3 H, OMe), 3.15 (dd, J = 2.4, 3.4 Hz, 1 H, 4-H), 1.81 (s, 3 H, $OCOCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 135.4, 130.7 (2 C), 129.7, 127.8 (2 C), 127.2, 127.1, 114.5, 74.6, 59.3, 56.6, 52.0, 49.8, 48.2, 20.6 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740 (C=O), 1600, 1480, 1440, 1360, 1220, 1120, 1040 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{17}H_{18}Cl_2O_4$ $[M]^+$ 356.0582; found 356.0584.

General Procedure for Hydrolysis of Dihalonorbornyl Acetates 8

5,6-Dibromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-ol (9a): K_2CO_3 (142 mg, 1.03 mmol) was added to a solution of **8a** (400 mg, 0.97 mmol) in MeOH (5 mL) and the mixture was stirred at room temperature for 20 h. After complete consumption of starting material (TLC monitoring) the solvent was evaporated under reduced pressure, water (10 mL) was added to the residue, and the aqueous layer was extracted three times with EtOAc (3 × 20 mL). The combined organic layer was then washed with brine and dried with anhydrous Na_2SO_4. The solvent was evaporated off under vacuum to leave a residue which was chromatographed on silica gel to afford the alcohol **9a**. R_f = 0.4 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 328 mg, 91%; solid, m.p. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.60 (dd, J = 4.1, 7.8 Hz, 1 H, 2-H_{exo}), 3.28 (dd, J = 2.2, 4.1 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.13 (s, 3 H, OMe), 3.05 (dd, J = 2.2, 3.4 Hz, 1 H, 4-H), 2.46–2.42 (m, 1 H, 3-H_{exo}), 1.46–1.29 (m, 4 H, OH peak buried under the peaks of 3 H of alkyl chain), 1.16–1.12 (m, 1 H), 0.92 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.6, 118.1, 115.0, 72.1, 60.5, 58.1, 51.9, 49.6, 42.2, 28.0, 21.9, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 3400 (OH), 2900, 1580, 1440, 1240, 1020, 840 cm^{-1}.

5,6-Dibromo-3-butyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (9b): R_f = 0.4 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 318 mg, 91% from **8b**; solid, m.p. 74–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59 (dd, J = 4.2, 7.6 Hz, 1 H, 2-H_{exo}), 3.29 (dd, J = 2.4, 4.2 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.13 (s, 3 H, OMe), 3.06 (dd, J = 2.2, 2.6 Hz, 1 H, 4-H), 2.45–2.39 (m, 1 H, 3-H_{exo}), 1.43–1.27 (m, 6 H, OH peak buried under the peaks of 5 H of alkyl chain), 1.19–1.11 (m, 1 H), 0.89 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.6, 118.1, 115.0, 72.1, 60.5, 58.0, 51.9, 49.6, 42.4, 30.9, 25.5, 22.8, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3450 (OH), 2950, 1580, 1460, 1260, 1040 cm^{-1}.

5,6-Dibromo-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-ol (9c): R_f = 0.4 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 352 mg, 95% from **8c**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59 (dd, J = 4.2, 7.6 Hz, 1 H, 2-H_{exo}), 3.29 (dd, J = 2.3, 4.0 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.13 (s, 3 H, OMe), 3.06 (dd, J = 2.4, 3.4 Hz, 1 H, 4-H), 2.45–2.39 (m, 1 H, 3-H_{exo}), 1.44–1.09 (m, 9 H, OH peak buried under the peaks of 8 H of alkyl chain), 0.87 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.7, 118.1, 115.0, 72.2, 60.5, 58.1, 51.9, 49.6, 42.5, 31.9, 28.4, 25.8, 22.5, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{22}Br_2O_3$ $[M]^+$ 395.9936; found 395.9936.

5,6-Dibromo-7,7-dimethoxy-3-hexylbicyclo[2.2.1]hept-5-en-2-ol (9d): R_f = 0.4 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 328 mg, 93% from **8d**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.55 (dd, J = 4.2, 7.6 Hz, 1 H, 2-H_{exo}), 3.24 (dd, J = 2.2, 4.2 Hz, 1 H, 1-H), 3.13 (s, 3 H, OMe), 3.09 (s, 3 H, OMe), 3.02 (br. t, J = 2.8 Hz, 1 H, 4-H), 2.41–2.34 (m, 1 H, 3-H_{exo}), 1.38–1.23 (m, 10 H, OH peak buried under the peaks of 9 H of alkyl chain), 1.13–1.08 (m, 1 H), 0.82 (t, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 122.7, 118.0, 115.0, 72.2, 60.5, 58.1, 51.9, 49.6, 42.5, 31.7, 29.4, 28.7, 25.8, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2900, 1580, 1440, 1240, 1040 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{15}H_{24}Br_2O_3$ $[M]^+$ 410.0092; found 410.0091.

5,6-Dibromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-ol (9e): R_f = 0.4 [EtOAc/hexane 10% (over 7% $AgNO_3$-impregnated silica gel)]; yield 402 mg, 99% from **8e**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.18 (m, 5 H, Ph), 4.83 (dd, J = 4.1, 7.6 Hz, 1 H, 2-H_{exo}), 3.69 (dd, J = 3.4, 7.6 Hz, 1 H, 3-H_{exo}), 3.43 (dd, J = 2.3, 4.0 Hz, 1 H, 1-H), 3.19 (br. t, J = 2.9 Hz, 1 H, 4-H), 3.18 (s, 3 H, OMe), 3.17 (s, 3 H, OMe), 1.41 (br. s, 1 H, D_2O exchangeable, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 131.2 (2 C), 128.2 (2 C), 127.2, 122.8, 120.7, 115.4, 73.0, 60.6 (2 C), 52.1, 49.8, 48.9 ppm. IR (neat): $\tilde{\nu}$ = 3300 (OH), 2900, 1580, 1480, 1440, 1260, 1040 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{15}H_{16}Br_2O_3$ $[M]^+$ 401.9466; found 401.9465.

5,6-Dibromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (9f): R_f = 0.3 [EtOAc/hexane 15% (over 7% $AgNO_3$-impregnated silica gel)]; yield 319 mg, 90% from **8f**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (ddd, J = 2.8, 4.3, 7.1 Hz, 1 H, 2-H_{exo}), 3.23 (dd, J = 2.2, 3.9 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.11 (s, 3 H, OMe), 2.99 (dd, J = 2.1, 3.8 Hz, 1 H, 4-H), 2.30 (ddd, J = 4.1, 7.3, 12.8 Hz, 1 H, 3-H_{exo}), 1.71 (br. s, 1 H, D_2O exchangeable, OH), 1.08 (dd, J = 2.2, 12.7 Hz, 1 H, 3-H_{endo}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.1, 117.8, 116.2, 71.6, 59.6, 55.2, 52.1, 49.7, 35.1 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2900, 1580, 1440, 1240, 1020, 840 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_9H_{12}Br_2O_3$ $[M]^+$ 325.9153; found 325.9155.

5,6-Dichloro-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-ol (9g): R_f = 0.4 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 802 mg, 90% from **8g**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57 (dd, J = 4.0, 7.7 Hz, 1 H, 2-H_{exo}), 3.19 (dd, J = 2.4, 3.9 Hz, 1 H, 1-H), 3.17 (s, 3 H, OMe), 3.12 (s, 3 H, OMe), 2.97 (br. t, J = 2.9 Hz, 1 H, 4-H), 2.42–2.38 (m, 1 H, 3-H_{exo}), 1.51 (br. s, 1 H, D_2O exchangeable, OH), 1.42–1.28 (m, 3 H), 1.13–1.09 (m, 1 H), 0.91 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.2, 125.4, 114.2, 72.0, 58.7, 56.2, 51.7, 49.5, 42.0, 28.1, 21.8, 14.2 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2900, 1600, 1440, 1240, 1080, 1040, 980 cm^{-1}.

3-Butyl-5,6-dichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (9h): R_f = 0.4 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 240 mg, 91% from **8h**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.57 (dd, J = 4.2, 7.8 Hz, 1 H, 2-H_{exo}), 3.20 (dd, J = 2.3, 4.0 Hz, 1 H, 1-H), 3.18 (s, 3 H, OMe), 3.13 (s, 3 H, OMe), 2.98 (br. t, J = 2.9 Hz, 1 H, 4-H), 2.42–2.35 (m, 1 H, 3-

H_{exo}), 1.43 (br. s, 1 H, D_2O exchangeable, OH), 1.39–1.28 (m, 5 H), 1.14–1.11 (m, 1 H), 0.89 (t, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.3, 125.4, 114.3, 72.1, 58.7, 56.2, 51.7, 49.5, 42.3, 30.8, 25.6, 22.8, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2900, 1600, 1440, 1260, 1040 cm^{-1}. HRMS (ESI): *m*/*z*: calcd. for $C_{13}H_{21}Cl_2O_3$ $[M + H]^+$ 295.0868; found 295.0864.

5,6-Dichloro-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-ol (9i): R_f = 0.4 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 568 mg, 92% from **8i**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.57 (dd, J = 4.2, 7.8 Hz, 1 H, 2-H_{exo}), 3.20 (dd, J = 2.2, 3.9 Hz, 1 H, 1-H), 3.18 (s, 3 H, OMe), 3.13 (s, 3 H, OMe), 2.98 (br. t, J = 2.8 Hz, 1 H, 4-H), 2.41–2.37 (m, 1 H, 3-H_{exo}), 1.42–1.28 (m, 8 H, OH peak buried under the peaks of 7 H of alkyl chain), 1.15–1.09 (m, 1 H), 0.87 (t, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.3, 125.4, 114.3, 72.1, 58.8, 56.2, 51.8, 49.5, 42.4, 31.9, 28.3, 25.9, 22.5, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2900, 1600, 1440, 1260, 1040 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{22}Cl_2O_3$ $[M]^+$ 308.0946; found 308.0948.

5,6-Dichloro-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (9j): R_f = 0.4 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 448 mg, 92% from **8j**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.53 (dd, J = 4.2, 7.6 Hz, 1 H, 2-H_{exo}), 3.16 (dd, J = 2.4, 3.9 Hz, 1 H, 1-H), 3.13 (s, 3 H, OMe), 3.08 (s, 3 H, OMe), 2.94 (br. t, J = 2.9 Hz, 1 H, 4-H), 2.37–2.31 (m, 1 H, 3-H_{exo}), 1.37 (br. s, 1 H, D_2O exchangeable, OH), 1.32–1.22 (m, 9 H), 1.11–1.06 (m, 1 H), 0.81 (t, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.3, 125.4, 114.3, 72.1, 58.7, 56.2, 51.8, 49.5, 42.4, 31.7, 29.4, 28.6, 25.9, 22.6, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2900, 1600, 1440, 1260, 1040 cm^{-1}. $C_{15}H_{24}Cl_2O_3$ (323.26): calcd. C 55.73, H 7.48; found C 55.69, H 7.21.

5,6-Dichloro-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-ol (9k): R_f = 0.5 [EtOAc/hexane 10% (over 7% $AgNO_3$-impregnated silica gel)]; yield 158 mg, 90% from cycloadduct **8k**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.20 (m, 5 H, Ph), 4.82 (dd, J = 4.1, 7.6 Hz, 1 H, 2-H_{exo}), 3.71 (dd, J = 3.4, 7.6 Hz, 1 H, 3-H_{exo}), 3.37 (dd, J = 2.4, 4.2 Hz, 1 H, 1-H), 3.20 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 3.16 (dd, J = 2.5, 3.3 Hz, 1 H, 4-H), 1.41 (br. s, 1 H, D_2O exchangeable, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3, 130.8 (2 C), 129.3, 128.2 (2 C), 127.8, 127.2, 114.7, 72.9 (2 C), 51.9, 58.7, 49.7, 48.8 ppm. IR (neat): $\tilde{\nu}$ = 3500 (OH), 2900, 1600, 1500, 1460, 1260, 1060 cm^{-1}.

General Procedure for Oxidation of Alcohols 9

5,6-Dibromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-one (7a): CrO_3 (504 mg, 5.04 mmol) was added to a solution of pyridine (798 mg, 10.1 mmol) in CH_2Cl_2 (20 mL) and the mixture was stirred at room temperature for 30 min. A solution of the alcohol **9a** (280 mg, 0.76 mmol) in CH_2Cl_2 (20 mL) was added to this deep-brown-colored mixture, which was stirred at room temperature for 40 h. The reaction mixture was then filtered 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 keto compound **7a**. R_f = 0.7 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 250 mg, 90%; white solid, m.p. 56–58 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.31–3.29 (m, 2 H, 1-H, 4-H), 3.22 (s, 3 H, OMe), 3.16 (s, 3 H, OMe), 2.43–2.39 (m, 1 H, 3-H_{exo}), 1.71–1.63 (m, 1 H), 1.45–1.31 (m, 2 H), 1.24–1.17 (m, 1 H), 0.86 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 127.5, 117.3, 114.5, 67.6, 56.7, 52.2, 50.1, 46.0, 30.6, 21.5, 13.6 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1750 (C=O), 1550, 1440, 1160, 1100, 960 cm^{-1}.

5,6-Dibromo-3-butyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (7b): R_f = 0.7 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 262 mg, 91% from alcohol **9b**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.36–3.33 (m, 2 H, 1-H, 4-H), 3.26 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 2.46–2.41 (m, 1 H, 3-H_{exo}), 1.78–1.73 (m, 1 H), 1.43–1.21 (m, 5 H), 0.89 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 127.5, 117.3, 114.5, 67.6, 56.7, 52.2, 50.1, 46.3, 30.5, 28.2, 22.3, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1750 (C=O), 1580, 1460, 1260, 1100 cm^{-1}.

5,6-Dibromo-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-one (7c): R_f = 0.7 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; 224 mg, yield 91% from alcohol **9c**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.35–3.34 (m, 2 H, 1-H, 4-H), 3.26 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 2.46–2.41 (m, 1 H, 3-H_{exo}) 1.79–1.71 (m, 1 H), 1.47–1.20 (m, 7 H), 0.87 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 127.5, 117.3, 114.5, 67.6, 56.6, 52.2, 50.1, 46.3, 31.4, 28.5, 27.9, 22.4, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740 (C=O), 1580, 1440, 1240, 1100, 1060, 980 cm^{-1}.

5,6-Dibromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (7d): R_f = 0.7 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 199 mg, 90% from alcohol **9d**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.36–3.33 (m, 2 H, 1-H, 4-H), 3.26 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 2.46–2.41 (m, 1 H, 3-H_{exo}), 1.79–1.71 (m, 1 H), 1.45–1.18 (m, 9 H), 0.86 (t, J = 6.59 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 127.5, 117.3, 114.5, 67.7, 56.7, 52.2, 50.1, 46.3, 31.5, 28.9, 28.6, 28.3, 22.6, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740 (C=O), 1580, 1440, 1260, 1060 cm^{-1}.

5,6-Dibromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-one (7e): R_f = 0.7 [EtOAc/hexane 10% (over 7% $AgNO_3$-impregnated silica gel)]; yield 410 mg, 92% from alcohol **9e**; solid, m.p. 108–110 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 3 H), 7.01–6.98 (m, 2 H), 3.93 (d, J = 3.6 Hz, 1 H, 3-H_{exo}), 3.57 (d, J = 2.7 Hz, 1 H, 1-H), 3.49 (dd, J = 2.6, 3.5 Hz, 1 H, 4-H), 3.33 (s, 3 H, OMe), 3.31 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 135.3, 128.8 (2 C), 128.51 (2 C), 128.48, 127.4, 116.4, 113.9, 68.4, 60.2, 52.2, 50.9, 50.4 ppm. IR (KBr): $\tilde{\nu}$ = 3500 (OH), 2900, 1600, 1500, 1460, 1260, 1060 cm^{-1}.

5,6-Dibromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (7f): R_f = 0.6 [EtOAc/hexane 15% (over 7% $AgNO_3$-impregnated silica gel)]; yield 259 mg, 90% from alcohol **9f**; white solid, m.p. 64–66 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.33 (d, J = 2.7 Hz, 1 H, 1-H), 3.31 (d, J = 2.7 Hz, 1 H, 4-H), 3.27 (s, 3 H, OMe), 3.21 (s, 3 H, OMe), 2.29 (dd, J = 3.0, 19.9 Hz, 1 H, 3-H_{exo}), 2.06 (d, J = 16.8 Hz, 1 H, 3-H_{endo}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7, 129.5, 117.2, 114.8, 67.2, 54.1, 52.4, 50.3, 34.8 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1740 (C=O), 1580, 1440, 1400, 1240, 1200, 1160, 1120, 1040, 1020, 980, 820 cm^{-1}.

5,6-Dichloro-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-one (7g): R_f = 0.7 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 652 mg, 91% from alcohol **9g**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.28–3.25 (m, 2 H, 1-H, 4-H) overlapping with 3.27 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 2.47–2.43 (m, 1 H, 3-H_{exo}), 1.74–1.69 (m, 1 H), 1.48–1.37 (m, 2 H), 1.26–1.19 (m, 1 H), 0.89 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 134.2, 122.4, 116.5, 65.5, 54.8, 52.1, 50.0, 45.9, 30.6, 21.4, 13.7 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740 (C=O), 1600, 1440, 1260, 1040, 980 cm^{-1}. HRMS (ESI): *m*/*z*: calcd. for $C_{12}H_{17}Cl_2O_3$ $[M + H]^+$ 279.0555; found 279.0558.

3-Butyl-5,6-dichloro-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (7h): R_f = 0.7 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated

silica gel)]; yield 180 mg, 90% from alcohol **9h**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.24–3.23 (m, 2 H, 1-H, 4-H) overlapping with 3.23 (s, 3 H, OMe), 3.15 (s, 3 H, OMe), 2.41–2.36 (m, 1 H, 3-H$_{exo}$), 1.76–1.68 (m, 1 H), 1.39–1.14 (m, 5 H), 0.84 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 134.2, 122.4, 116.5, 65.6, 54.9, 52.2, 50.0, 46.3, 30.4, 28.3, 22.3, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740 (C=O), 1600, 1440, 1240, 1040, 980 cm^{-1}. HRMS (ESI): m/z: calcd. for $C_{13}H_{19}Cl_2O_3$ $[M + H]^+$ 293.0711; found 293.0711.

5,6-Dichloro-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-one (7i): R_f = 0.7 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 458 mg, 92% from alcohol **9i**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (broad peak, 2 H, 1-H, 4-H) overlapping with 3.27 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 2.45–2.42 (m, 1 H, 3-H$_{exo}$), 1.78–1.72 (m, 1 H), 1.45–1.19 (m, 7 H), 0.86 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 134.2, 122.4, 116.5, 65.5, 54.7, 52.1, 49.9, 46.2, 31.4, 28.5, 27.9, 22.3, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740 (C=O), 1600, 1440, 1240, 1040, 980 cm^{-1}.

5,6-Dichloro-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (7j): R_f = 0.7 [EtOAc/hexane 4% (over 7% $AgNO_3$-impregnated silica gel)]; yield 355 mg, 94% from alcohol **9j**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (broad peak, 2 H, 1-H, 4-H) overlapping with 3.27 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 2.45–2.41 (m, 1 H, 3-H$_{exo}$), 1.79–1.71 (m, 1 H), 1.44–1.17 (m, 9 H), 0.86 (t, J = 6.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 134.2, 122.4, 116.5, 65.6, 54.8, 52.1, 50.0, 46.2, 31.5, 28.9, 28.6, 28.1, 22.5, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740 (C=O), 1600, 1440, 1260, 1160, 1120, 1040 cm^{-1}.

5,6-Dichloro-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-one (7k): R_f = 0.80 [EtOAc/hexane 10% (over 7% $AgNO_3$-impregnated silica gel)]; yield 90 mg, 91% from alcohol **9k**; solid, m.p. 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.21 (m, 3 H), 6.99–6.98 (m, 2 H), 3.89 (d, J = 3.4 Hz, 1 H, 3-H$_{exo}$), 3.48 (d, J = 2.7 Hz, 1 H, 1-H), 3.39 (dd, J = 2.7, 3.7 Hz, 1 H, 4-H), 3.30 (s, 3 H, OMe), 3.29 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.6, 135.3, 134.9, 128.6 (4 C), 127.5, 121.9, 115.8, 66.4, 58.4, 52.2, 51.1, 50.3 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1740 (C=O), 1600, 1500, 1440, 1260, 1220, 1160, 1100, 1060, 980, 960, 900 cm^{-1}.

Procedure for Fragmentation of Ketones 7 to Afford the Substituted *meta*-Halophenols 10 and Their Methyl Ether Derivatives 11

Methyl 5-Bromo-3-hydroxy-2-propylbenzoate (10a) and Methyl 5-Bromo-3-methoxy-2-propylbenzoate (11a): *para*-Toluenesulfonic acid monohydrate (84 mg, 0.44 mmol) was added to a solution of the ketone **7a** (162 mg, 0.44 mmol) in toluene (6 mL) and the reaction mixture was heated to reflux at 110–120 °C for 10 h. The end of the reaction was monitored by TLC with the disappearance of the ketone **7a**. The reaction mixture was diluted with water (5 mL) and the aqueous layer was extracted three times with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4. Solvent was removed in vacuo to furnish a residue, which was purified by silica gel column chromatography to afford methyl 5-bromo-3-hydroxy-2-propylbenzoate (**10a**) and methyl 5-bromo-3-methoxy-2-propylbenzoate (**11a**).

Compound 10a: R_f = 0.5 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 72 mg, 60% from ketone **7a**; solid, m.p. 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 2.0 Hz, 1 H, Ar-H), 7.07 (d, J = 1.9 Hz, 1 H, Ar-H), 3.82 (s, 3 H, OMe), 2.81 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 1.58–1.50 (m, 2 H), 0.95 (t, J = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 155.3, 132.9, 129.9, 125.4, 121.7, 119.0, 52.6, 28.5, 23.3, 14.4 ppm. IR (KBr): $\tilde{\nu}$ = 3200 (OH), 2900, 1680 (C=O), 1560, 1440, 1400, 1340, 1260, 1200, 1060, 1000, 940, 840 cm^{-1}. $C_{11}H_{13}BrO_3$ (273.13): calcd. C 48.37, H 4.80; found C 48.35, H 4.67.

Compound 11a: R_f = 0.8 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 38 mg, 30% from ketone **7a**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 2.0 Hz, 1 H, Ar-H), 7.01 (d, J = 1.7 Hz, 1 H, Ar-H), 3.81 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 2.75 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 1.49–1.42 (m, 2 H), 0.88 (t, J = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 158.6, 132.6, 132.3, 124.5, 119.2, 116.6, 55.9, 52.2, 28.4, 23.2, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440, 1380, 1240, 1220, 1180, 1060, 1040, 880, 820 cm^{-1}. $C_{12}H_{15}BrO_3$ (287.15): calcd. C 50.19, H 5.27; found C 50.48, H 5.22.

Methyl 5-Bromo-2-butyl-3-hydroxybenzoate (10b): R_f = 0.5 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 55 mg, 49% from ketone **7b**; white solid, m.p. 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, J = 2.0 Hz, 1 H, Ar-H), 7.06 (d, J = 2.2 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OMe), 2.83 (t, J = 7.9 Hz, 2 H, $ArCH_2$), 1.54–1.46 (m, 2 H), 1.42–1.35 (m, 2 H), 0.90 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 155.0, 132.7, 129.8, 125.3, 121.5, 118.8, 52.4, 31.9, 26.2, 22.9, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1560, 1440, 1400, 1260, 1200, 1060, 1000, 940, 840 cm^{-1}. HRMS (EI): m/z: calcd. for $C_{12}H_{15}BrO_3$ $[M]^+$ 286.0204; found 286.0207.

Methyl 5-Bromo-2-butyl-3-methoxybenzoate (11b): R_f = 0.8 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 42 mg, 36% from ketone **7b**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 2.0 Hz, 1 H, Ar-H), 7.05 (d, J = 2.0 Hz, 1 H, Ar-H), 3.86 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 2.82 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 1.48–1.30 (m, 4 H), 0.89 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 158.6, 132.6, 132.5, 124.6, 119.1, 116.6, 55.9, 52.2, 32.2, 26.2, 22.9, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440, 1400, 1240, 1040, 820, 720 cm^{-1}. HRMS (EI): m/z: calcd. for $C_{13}H_{17}BrO_3$ $[M]^+$ 300.0361; found 300.0364.

Methyl 5-Bromo-3-hydroxy-2-pentylbenzoate (10c): R_f = 0.5 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 68 mg, 53% from ketone **7c**; white solid, m.p. 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 2.0 Hz, 1 H, Ar-H), 7.01 (d, J = 2.2 Hz, 1 H, Ar-H), 3.82 (s, 3 H, OMe), 2.77 (t, J = 8.1 Hz, 2 H, $ArCH_2$), 1.49–1.43 (m, 2 H), 1.30–1.23 (m, 4 H), 0.82 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 154.9, 132.7, 129.9, 125.4, 121.5, 118.8, 52.3, 32.0, 29.5, 26.4, 22.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1680 (C=O), 1560, 1420, 1400, 1340, 1280, 1220, 1080, 1000, 920, 860 cm^{-1}. $C_{13}H_{17}BrO_3$ (301.18): calcd. C 51.84, H 5.69; found C 52.05, H 5.57.

Methyl 5-Bromo-3-methoxy-2-pentylbenzoate (11c): R_f = 0.8 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 50 mg, 37% from ketone **7c**; white solid, m.p. 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 1.9 Hz, 1 H, Ar-H), 7.05 (d, J = 2.0 Hz, 1 H, Ar-H), 3.85 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 2.81 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 1.50–1.43 (m, 2 H), 1.35–1.29 (m, 4 H), 0.87 (t, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 158.5, 132.5, 132.4, 124.5, 119.1, 116.6, 55.9, 52.2, 32.1, 29.6, 26.4, 22.4, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440, 1400, 1240, 1040, 820, 720 cm^{-1}.

Methyl 5-Bromo-2-hexyl-3-hydroxybenzoate (10d): R_f = 0.5 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 92 mg, 56% from ketone **7d**; viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.43 (d, J = 2.0 Hz, 1 H, Ar-H), 7.01 (d, J = 2.0 Hz, 1 H, Ar-H), 3.82 (s, 3 H, OMe), 2.76 (t, J = 7.9 Hz, 2 H, $ArCH_2$), 1.49–1.41 (m, 2 H), 1.33–1.19 (m, 6 H), 0.79 (t, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 155.1, 132.6, 129.9, 125.2, 121.5, 118.8, 52.4, 31.6, 29.8, 29.6, 26.5, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1560, 1420, 1400, 1260, 1080, 1000, 900, 840, 720 cm^{-1}. $C_{14}H_{19}BrO_3$ (315.21): calcd. C 53.35, H 6.08; found C 53.71, H 5.98.

Methyl 5-Bromo-2-hexyl-3-methoxybenzoate (11d): R_f = 0.8 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 54 mg, 32% from ketone **7d**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 1.7 Hz, 1 H, Ar-H), 7.00 (d, J = 1.7 Hz, 1 H, Ar-H), 3.80 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 2.75 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 1.44–1.37 (m, 2 H), 1.31–1.22 (m, 6 H), 0.81 (t, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 158.5, 132.6, 132.5, 124.5, 119.1, 116.6, 55.9, 52.2, 31.6, 29.9, 29.6, 26.5, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440, 1400, 1240, 1040, 820, 720 cm^{-1}. $C_{15}H_{21}BrO_3$ (329.23): calcd. C 54.72, H 6.43; found C 55.07, H 6.30.

Methyl 5-Bromo-3-hydroxy-2-phenylbenzoate (10e): R_f = 0.5 [EtOAc/hexane 12% (over 7% $AgNO_3$-impregnated silica gel)]; yield 86 mg, 51% from ketone **7e**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, J = 1.9 Hz, 1 H, Ar-H), 7.45–7.37 (m, 3 H), 7.24 (d, J = 2.0 Hz, 1 H, Ar-H), 7.20–7.18 (m, 2 H), 3.53 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 154.1, 133.7, 132.5, 129.3 (2 C), 129.2 (2 C), 128.6, 127.5, 124.9, 121.9, 121.8, 52.2 ppm. IR (neat): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1400, 1280, 1140, 1000, 920, 900, 840 cm^{-1}. $C_{14}H_{11}BrO_3$ (307.14): calcd. C 54.75, H 3.61; found C 54.69, H 3.57.

Methyl 4-Bromo-6-methoxybiphenyl-2-carboxylate (11e): R_f = 0.8 [EtOAc/hexane 12% (over 7% $AgNO_3$-impregnated silica gel)]; yield 56 mg, 32% from ketone **7e**; solid, m.p. 106–108 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, J = 2.0 Hz, 1 H, Ar-H), 7.44–7.38 (m, 3 H), 7.26 (d, J = 1.7 Hz, 1 H, Ar-H), 7.25–7.24 (m, 2 H), 3.78 (s, 3 H, OMe), 3.58 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 157.6, 135.6, 134.3, 130.1, 129.3 (2 C), 127.7 (2 C), 127.4, 124.1, 121.5, 116.9, 56.2, 52.1 ppm. IR (KBr): $\tilde{\nu}$ = 1700 (C=O), 1560, 1440, 1400, 1300, 1260, 1180, 1040, 880, 840 cm^{-1}. HRMS (EI): m/z: calcd. for $C_{15}H_{13}BrO_3$ $[M]^+$ 320.0048; found 320.0048.

Methyl 3-Bromo-5-hydroxybenzoate (10f): R_f = 0.4 [EtOAc/hexane 15% (over 7% $AgNO_3$-impregnated silica gel)]; yield 60 mg, 42% from ketone **7f**; solid, m.p. 124–126 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (br. d, J = 1.4 Hz, 1 H, Ar-H), 7.42 (br. d, J = 1.0 Hz, 1 H, Ar-H), 7.16 (br. d, J = 2.4 Hz, 1 H, Ar-H), 5.85 (br. s, 1 H, D_2O exchangeable, OH), 3.85 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 156.7, 132.4, 124.8, 123.5, 122.9, 115.4, 52.8 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1580, 1420, 1300, 1260, 1220, 1180, 1100, 980, 900, 860, 820 cm^{-1}. $C_8H_7BrO_3$ (231.05): calcd. C 41.59, H 3.05; found C 41.67, H 2.98.

Methyl 3-Bromo-5-methoxybenzoate (11f): R_f = 0.7 [EtOAc/hexane 15% (over 7% $AgNO_3$-impregnated silica gel)]; yield 24 mg, 16% from ketone **7f**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (t, J = 1.5 Hz, 1 H, Ar-H), 7.42 (dd, J = 1.3, 2.3 Hz, 1 H, Ar-H), 7.17 (t, J = 2.1 Hz, 1 H, Ar-H), 3.85 (s, 3 H, OMe), 3.77 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 160.2, 132.7, 124.9, 122.7, 122.2, 113.5, 55.8, 52.5 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440, 1380, 1240, 1220, 1180, 1060 cm^{-1}. HRMS (EI): m/z: calcd. for $C_9H_9BrO_3$ $[M]^+$ 243.9735; found 243.9736.

Methyl 5-Chloro-3-hydroxy-2-propylbenzoate (10g): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 58 mg, 48% from ketone **7g**; solid, m.p. 78–80 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 2.2 Hz, 1 H, Ar-H), 6.92 (d, J = 2.2 Hz, 1 H), 5.42 (br. s, 1 H, D_2O exchangeable, OH), 3.87 (s, 3 H, OMe), 2.82 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 1.58–1.52 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 154.9, 132.4, 131.4, 129.1, 122.4, 118.6, 52.4, 28.3, 23.2, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1680 (C=O), 1560, 1440, 1400, 1340, 1280, 1200, 1080, 1000, 920, 860 cm^{-1}. $C_{11}H_{13}ClO_3$ (228.67): calcd. C 57.78, H 5.73; found C 57.60, H 5.65.

Methyl 5-Chloro-3-methoxy-2-propylbenzoate (11g): R_f = 0.9 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 44 mg, 35% from ketone **7g**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 2.0 Hz, 1 H, Ar-H), 6.92 (d, J = 1.7 Hz, 1 H, Ar-H), 3.86 (s, 3 H, OMe), 3.80 (s, 3 H, OMe), 2.81 (t, J = 7.8 Hz, 2 H, $ArCH_2$), 1.54–1.47 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 158.6, 132.3, 131.7, 131.6, 121.6, 113.8, 55.9, 52.2, 28.3, 23.3, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1580, 1440, 1400, 1220, 1180, 1040, 880, 840 cm^{-1}.

Methyl 2-Butyl-5-chloro-3-hydroxybenzoate (10h): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 52 mg, 44% from ketone **7h**; solid, m.p. 86–88 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 2.2 Hz, 1 H, Ar-H), 6.92 (d, J = 2.0 Hz, 1 H, Ar-H), 3.87 (s, 3 H, OMe), 2.84 (t, J = 7.9 Hz, 2 H, $ArCH_2$), 1.54–1.46 (m, 2 H), 1.42–1.33 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 154.9, 132.4, 131.4, 129.3, 122.5, 118.6, 52.3, 32.1, 26.2, 22.9, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1680 (C=O), 1560, 1420, 1400, 1320, 1220, 1180, 1080, 1000, 920, 900, 840 cm^{-1}. $C_{12}H_{15}ClO_3$ (242.70): calcd. C 59.39, H 6.23; found C 59.33, H 6.10.

Methyl 2-Butyl-5-chloro-3-methoxybenzoate (11h): R_f = 0.9 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 47 mg, 37% from ketone **7h**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 2.2 Hz, 1 H, Ar-H), 6.86 (d, J = 2.0 Hz, 1 H, Ar-H), 3.82 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 2.77 (t, J = 7.7 Hz, 2 H, $ArCH_2$), 1.43–1.27 (m, 4 H), 0.85 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 158.5, 132.2, 131.9, 131.5, 121.6, 113.8, 55.9, 52.2, 32.2, 26.1, 22.9, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1720 (C=O), 1560, 1440, 1400, 1260, 1240, 1040, 880, 840 cm^{-1}. $C_{13}H_{17}ClO_3$ (256.73): calcd. C 60.82, H 6.67; found C 60.36, H 6.51.

Methyl 5-Chloro-3-hydroxy-2-pentylbenzoate (10i): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 50 mg, 41% from ketone **7i**; solid, m.p. 54–56 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, J = 2.2 Hz, 1 H, Ar-H), 6.87 (d, J = 2.2 Hz, 1 H, Ar-H), 5.14 (br. s, 1 H, D_2O exchangeable, OH), 3.82 (s, 3 H, OMe), 2.78 (t, J = 7.9 Hz, 2 H, $ArCH_2$), 1.49–1.43 (m, 2 H), 1.31–1.24 (m, 4 H), 0.82 (t, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 154.8, 132.5, 131.4, 129.3, 122.6, 118.6, 52.3, 32.0, 29.6, 26.4, 22.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1680 (C=O), 1560, 1440, 1400, 1280, 1220, 1180, 1080, 1000, 920, 840 cm^{-1}. $C_{13}H_{17}ClO_3$ (256.73): calcd. C 60.82, H 6.67; found C 60.71, H 6.56.

Methyl 5-Chloro-3-methoxy-2-pentylbenzoate (11i): R_f = 0.9 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 50 mg, 39% from ketone **7i**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, J = 2.0 Hz, 1 H, Ar-H), 6.86 (d, J = 2.0 Hz, 1 H, Ar-H), 3.80 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 2.76 (t, J = 7.9 Hz, 2 H, $ArCH_2$), 1.43–1.39 (m, 2 H), 1.28–1.24 (m, 4 H), 0.82 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 158.5, 132.2, 131.9, 131.5, 121.6, 113.8, 55.9, 52.2, 32.1, 29.7, 26.3, 22.4, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440,

1400, 1260, 1040, 880, 840 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{19}ClO_3$ $[M]^+$ 270.1023; found 270.1020.

Methyl 5-Chloro-2-hexyl-3-hydroxybenzoate (10j): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 45 mg, 45% from ketone **7j**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 2.0 Hz, 1 H, Ar-H), 6.87 (d, *J* = 2.2 Hz, 1 H, Ar-H), 5.21 (br. s, 1 H, D_2O exchangeable, OH), 3.82 (s, 3 H, OMe), 2.78 (t, *J* = 7.9 Hz, 2 H, $ArCH_2$), 1.48–1.42 (m, 2 H), 1.33–1.21 (m, 6 H), 0.81 (t, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 154.8, 132.4, 131.4, 129.3, 122.5, 118.6, 52.3, 31.6, 29.9, 29.6, 26.4, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1560, 1420, 1400, 1280, 1220, 1080, 1000, 920, 840 cm^{-1}. $C_{14}H_{19}ClO_3$ (270.76): calcd. C 62.10, H 7.07; found C 61.82, H 6.91.

Methyl 5-Chloro-2-hexyl-3-methoxybenzoate (11j): R_f = 0.9 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 41 mg, 38% from ketone **7j**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 2.2 Hz, 1 H, Ar-H), 6.87 (d, *J* = 2.0 Hz, 1 H, Ar-H), 3.81 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 2.76 (t, *J* = 7.8 Hz, 2 H, $ArCH_2$), 1.43–1.37 (m, 2 H), 1.29–1.18 (m, 6 H), 0.81 (t, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 158.5, 132.2, 131.9, 131.5, 121.6, 113.8, 55.9, 52.2, 31.6, 30.0, 29.6, 26.4, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440, 1400, 1040, 880, 840, 720 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{15}H_{21}ClO_3$ $[M]^+$ 284.1179; found 284.1173.

Methyl 4-Chloro-6-hydroxybiphenyl-2-carboxylate (10k): R_f = 0.6 [EtOAc/hexane 12% (over 7% $AgNO_3$-impregnated silica gel)]; yield 46 mg, 44% from ketone **7k**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.41 (m, 5 H), 7.25–7.23 (m, 1 H), 7.14 (d, *J* = 2.0 Hz, 1 H, Ar-H), 5.23 (br. s, 1 H, OH), 3.58 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 154.0, 134.3, 133.7, 132.3, 129.3 (4 C), 128.7, 127.0, 122.1, 119.1, 52.1 ppm. IR (neat): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1400, 1280, 1140, 1000, 920, 900, 840 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{11}ClO_3$ $[M]^+$ 262.0397; found 262.0392.

Methyl 4-Chloro-6-methoxybiphenyl-2-carboxylate (11k): R_f = 0.9 [EtOAc/hexane 12% (over 7% $AgNO_3$-impregnated silica gel)]; yield 40 mg, 39% from ketone **7k**; solid, m.p. 108–110 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.34 (m, 5 H), 7.24 (d, *J* = 1.7 Hz, 1 H, Ar-H), 7.08 (d, *J* = 2.0 Hz, 1 H, Ar-H), 3.77 (s, 3 H, OMe), 3.56 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 157.6, 135.7, 134.0, 133.9, 129.7, 129.4 (2 C), 127.8 (2 C), 127.4, 121.2, 114.2, 56.2, 52.1 ppm. IR (KBr): $\tilde{\nu}$ = 1720 (C=O), 1560, 1440, 1400, 1300, 1260, 1180, 1040, 880, 840 cm^{-1}. HRMS (EI): *m*/*z*: calcd. for $C_{15}H_{13}ClO_3$ $[M]^+$ 276.0553; found 276.0553.

Methyl 4-Bromo-6-ethoxybiphenyl-2-carboxylate (12): R_f = 0.8 [EtOAc/hexane 12% (over 7% $AgNO_3$-impregnated silica gel)]; yield 6 mg, 7% from ketone **7e**; solid, m.p. 88–90 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 1.7 Hz, 1 H, Ar-H), 7.32–7.23 (m, 3 H), 7.15–7.11 (m, 3 H), 3.89 (q, *J* = 7.0 Hz, 2 H, OCH_2), 3.47 (s, 3 H, OMe), 1.17 (t, *J* = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 156.9, 135.8, 134.4, 130.5, 129.3 (2 C), 127.6 (2 C), 127.2, 124.1, 121.4, 118.3, 64.8, 52.1, 14.4 ppm. IR (KBr): $\tilde{\nu}$ = 1720 (C=O), 1560, 1440, 1400, 1300, 1260, 1180, 1040, 880, 840 cm^{-1}. $C_{16}H_{15}BrO_3$ (335.20): calcd. C 57.33, H 4.51; found C 57.34, H 4.47.

5,6-Dibromo-3-butyl-1,4-dideuterio-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (13): R_f = 0.6 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 216 mg, 72% from **4b**, viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.35 (d, *J* = 7.8 Hz, 1 H, 2-H_{exo}), 3.12 (s, 3 H, OMe), 3.11 (s, 3 H, OMe), 2.55–2.49 (m, 1 H, 3-H_{exo}), 1.96 (s, 3 H, $OCOCH_3$), 1.34–1.13 (m, 6 H), 0.83 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 121.7, 118.6, 114.9, 73.4, 57.8–57.1 (m, 2 C attached to D), 51.9, 49.7, 41.9, 30.7, 25.8, 22.7, 20.7, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1740 (C=O), 1580, 1460, 1370, 1210, 1040 cm^{-1}.

5,6-Dibromo-3-butyl-1,4-dideuterio-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (14): R_f = 0.4 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 168 mg, 90% from **13**, solid; m.p. 74–76 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.59 (d, *J* = 7.8 Hz, 1 H, 2-H_{exo}), 3.17 (s, 3 H, OMe), 3.13 (s, 3 H, OMe), 2.44–2.38 (m, 1 H, 3-H_{exo}), 1.45–1.13 (m, 7 H, OH peak buried under the peaks of 6 H of alkyl chain), 0.89 (t, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR: δ = 122.6, 118.0, 114.9, 72.1, 60.5–59.9 (m, C attached to D), 58.1–57.3 (m, C attached to D), 51.9, 49.6, 42.3, 30.9, 25.5, 22.8, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3450 (OH), 2950, 1580, 1460, 1260, 1040 cm^{-1}. HRMS (ESI): *m*/*z*: calcd. for $C_{13}H_{18}Br_2D_2NaO_3$ $[M + Na]^+$ 406.9802; found 406.9745.

5,6-Dibromo-3-butyl-1,4-dideuterio-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (15): R_f = 0.7 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 124 mg, 92% from alcohol **14**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.26 (s, 3 H, OMe), 3.19 (s, 3 H, OMe), 2.43 (dd, *J* = 4.6, 10.5 Hz, 1 H, 3-H_{exo}), 1.80–1.72 (m, 1 H), 1.45–1.18 (m, 5 H), 0.88 (t, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 127.5, 117.2, 114.4, 67.6–67.3 (m, C attached to D), 56.6–56.1 (m, C attached to D), 52.2, 50.1, 46.2, 30.5, 28.2, 22.3, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1750 (C=O), 1580, 1460, 1260, 1100 cm^{-1}.

Phenolic Compound 16: This compound was obtained from **15** by treatment with PTSA (Scheme 11): R_f = 0.5 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 42 mg, 48% from ketone **15**; solid, m.p. 96–98 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 1.7 Hz, 1 H, Ar-H), 7.06 (d, *J* = 2.0 Hz, 1 H, Ar-H), 5.37 (br. s, 1 H, OH), 3.87 (s, 3 H, OMe), 2.83 (t, *J* = 7.9 Hz, 2 H, $ArCH_2$), 1.54–1.46 (m, 2 H), 1.42–1.33 (m, 2 H), 0.91 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^3C NMR (100 MHz, $CDCl_3$): δ = 167.4, 155.0, 132.7, 129.8, 125.4, 121.5, 118.8, 52.4, 31.9, 26.2, 22.9, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1560, 1440, 1400, 1260, 1200, 1060, 1000, 940, 840 cm^{-1}. HRMS (ESI): *m*/*z*: calcd. for $C_{12}H_{15}BrNaO_3$ $[M + Na]^+$ 309.0102; found 309.0093.

Phenolic Ether 17: This compound was obtained from **15** by treatment with PTSA (Scheme 11): R_f = 0.8 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 30 mg, 32% from ketone **15**; viscous liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 0.8 Hz, 1 H, Ar-H), 7.00 (d, *J* = 1.2 Hz, 1 H, Ar-H), 3.81 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 2.77 (t, *J* = 7.8 Hz, 2 H, $ArCH_2$), 1.43–1.27 (m, 4 H), 0.85 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 158.6, 132.6, 132.5, 124.6, 119.1, 116.6, 55.9, 52.2, 32.2, 26.2, 22.9, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1700 (C=O), 1560, 1440, 1400, 1240, 1040, 820, 720 cm^{-1}. HRMS (ESI): *m*/*z*: calcd. for $C_{13}H_{18}BrO_3$ $[M + H]^+$ 301.0439; found 301.0439.

Phenolic Compound 18: This compound was obtained from **7b** by treatment with [D]TFA (Scheme 12): R_f = 0.5 [EtOAc/hexane 5% (over 7% $AgNO_3$-impregnated silica gel)]; yield 48 mg, 80% from ketone **7b**; solid, m.p. 96–98 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H, Ar-H of minor component), 7.01 (s, 1 H, Ar-H of minor component), 5.49 (br. s, 1 H, OH), 3.82 (s, 3 H, OMe), 2.78 (t, *J* = 7.8 Hz, 2 H, $ArCH_2$), 1.49–1.41 (m, 2 H), 1.37–1.28 (m, 2 H), 0.86 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 154.9, 132.5, 129.9, 125.4–124.8 (m, Ar-C-6 attached to D), 121.5–120.9 (m, Ar-C-4 attached to D), 118.6, 52.4, 31.9, 26.2, 22.9, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1700

(C=O), 1560, 1440, 1400, 1260, 1200, 1060, 1000, 940, 840 cm^{-1}. HRMS (ESI): *m*/*z*: calcd. for $C_{12}H_{13}BrD_2NaO_3$ $[M + Na]^+$ 311.0228; found 311.0204.

Supporting Information (see also footnote on the first page of this article): Five pages with graphics and related discussions; 75 pages with copies of ^1H and ^{13}C NMR spectra of all the compounds and HRMS spectra of some of the compounds.

Acknowledgments

We thank the Council of Scientific & Industrial Research (CSIR), New Delhi, for financial assistance. S.C. thanks the CSIR for a fellowship.

[1] a) S. Peters, P. Spiteller, *J. Nat. Prod.* **2006**, *69*, 1809–1812; b) Z. Ahmed, P. Langer, *Tetrahedron Lett.* **2006**, *47*, 417–419; c) K. Li, X.-M. Li, N.-Y. Ji, J. B. Gloer, B.-G. Wang, *Org. Lett.* **2008**, *10*, 1429–1432; d) X.-J. Duan, X.-M. Li, B.-G. Wang, *J. Nat. Prod.* **2007**, *70*, 1210–1213; e) M. Ma, J. Zhao, S. Wang, S. Li, Y. Yang, J. Shi, X. Fan, L. He, *J. Nat. Prod.* **2006**, *69*, 206–210; f) L. Lundgren, K. Olsson, O. Theander, *Acta Chem. Scand., Ser. B* **1979**, *B33*, 105–108; g) T. Hattori, A. Konno, K. Adachi, Y. Shizuri, *Fish. Sci.* **2001**, *67*, 899–903; h) H. Kurihara, T. Mitani, J. Kawabata, K. Takahashi, *J. Nat. Prod.* **1999**, *62*, 882–884; i) M. Pedersén, P. Saenger, L. Fries, *Phytochemistry* **1974**, *13*, 2273–2279.

[2] a) *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed., Wiley-VCH, Weinheim, **1998**, and references cited therein; b) J.-O. Levin, C.-A. Nilsson, *Chemosphere* **1977**, *6*, 443–448; c) E. R. Freiter, *Kirk–Othmer Encyclopedia of Chemical Technology*, vol. 5, 6th ed., John Wiley & Sons, New York, **1993**.

[3] a) H. Kurihara, T. Mitani, J. Kawabata, K. Takahashi, *Fish. Sci.* **1999**, *65*, 300–303; b) W. Wang, Y. Okada, H. Shi, Y. Wang, T. Okuyama, *J. Nat. Prod.* **2005**, *68*, 620–622; c) X. Fu, F. J. Schmitz, M. Govindan, S. A. Abbas, K. M. Hanson, P. A. Horton, P. Crews, M. Laney, R. C. Schatzman, *J. Nat. Prod.* **1995**, *58*, 1384–1391.

[4] K. Kurata, T. Amiya, *Phytochemistry* **1980**, *19*, 141–142.

[5] N. A. Shoeib, M. C. Bibby, G. Blunden, P. A. Linley, D. J. Swaine, R. T. Wheelhouse, C. W. Wright, *J. Nat. Prod.* **2004**, *67*, 1445–1449.

[6] J. S. Choi, H. J. Park, H. A. Jung, H. Y. Chung, J. H. Jung, W. C. Choi, *J. Nat. Prod.* **2000**, *63*, 1705–1706.

[7] J. L. Boyle, R. C. Lindsay, D. A. Stuiber, *J. Aquat. Food Prod. Technol.* **1993**, *2*, 75–112.

[8] a) F. B. Whitfield, F. Helidoniotis, K. J. Shaw, D. Svoronos, *J. Agric. Food Chem.* **1997**, *45*, 4398–4405; b) F. B. Whitfield, M. Drew, F. Helidoniotis, D. Svoronos, *J. Agric. Food Chem.* **1999**, *47*, 4756–4762.

[9] a) H. Y. Chung, W. C. J. Ma, J.-S. Kim, *J. Agric. Food Chem.* **2003**, *51*, 6752–6760; b) C. M. Olsen, E. T. M. Meussen-Elholm, J. A. Holme, J. K. Hongslo, *Toxicol. Lett.* **2002**, *129*, 55–63, and references therein.

[10] For the usefulness of phenolic derivatives as synthetic intermediates, see: a) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 4321–4326; b) J. J. J. Leathy, B. T. Golding, R. J. Griffin, I. R. Hardcastle, C. Richardson, L. Rigoreau, G. C. M. Smith, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6083–6087; c) S. Gobbi, A. Rampa, A. Bisi, F. Belluti, L. Piazzi, P. Valenti, A. Caputo, A. Zampiron, M. Carrara, *J. Med. Chem.* **2003**, *46*, 3662–3669; d) M. L. N. Rao, H. Houjou, K. Hiratani, *Tetrahedron Lett.* **2001**, *42*, 8351–8355; e) A. S. Klymchenko, T. Ozturk, V. G. Pivovarenko, A. P. Demchenko, *Tetrahedron Lett.* **2001**, *42*, 7967–7970; f) S. Ruchirawat, T. Mutarapat, *Tetrahedron Lett.* **2001**, *42*, 1205–1208; g) A. Fougerousse, E. Gonzalez, R. Brouillard, *J. Org. Chem.* **2000**, *65*, 583–586; h) G. T. Crisp, P. D. Turner, *Tetrahedron* **2000**, *56*, 407–415; i) C. Cimarelli, G. Palmeiri, *Tetrahedron* **1998**, *54*, 15711–15720.

[11] For various chlorination and bromination methods, see: a) J. M. Gnaim, R. A. Sheldon, *Tetrahedron Lett.* **2004**, *45*, 9397–9399; b) Y. Ogata, M. Kimura, Y. Kondo, H. Katoh, F.-C. Chen, *J. Chem. Soc. Perkin Trans. 2* **1984**, 451–453; c) L. Menini, E. V. Gusevskaya, *Chem. Commun.* **2006**, 209–211; d) H. A. Muathen, *Tetrahedron* **1996**, *52*, 8863–8866; e) V. Kavala, S. Naik, B. K. Patel, *J. Org. Chem.* **2005**, *70*, 4267–4271; f) S. Kajigaeshi, Y. Ueda, S. Fujisaki, T. Kakinami, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2096–2098; g) P. K. Chhattise, A. V. Ramaswamy, S. B. Waghmode, *Tetrahedron Lett.* **2008**, *49*, 189–194, and references therein.

[12] For the synthesis of polysubstituted phenolic derivatives, see: a) G. Chen, A. S. C. Chan, F. Y. Kwong, *Tetrahedron Lett.* **2007**, *48*, 473–476; b) K. W. Anderson, T. Ikawa, R. E. Tundel, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 10694–10695; c) F. Shi, M. R. Smith III, R. E. Maleczka Jr, *Org. Lett.* **2006**, *8*, 1411–1414; d) Y. Lee, M. J. Kelly, *Tetrahedron Lett.* **2006**, *47*, 4897–4901; e) A. Corma, V. Fornés, S. Iborra, M. Mifsud, M. Renz, *J. Catal.* **2004**, *221*, 67–76; f) J. F. Rogers, D. M. Green, *Tetrahedron Lett.* **2002**, *43*, 3585–3587; g) W. F. Austin, Y. Zhang, R. L. Danheiser, *Tetrahedron* **2008**, *64*, 915–925; h) D. Y. Park, S. J. Kim, T. H. Kim, J. N. Kim, *Tetrahedron Lett.* **2006**, *47*, 6315–6319; i) S. C. Kim, H. S. Lee, Y. J. Lee, J. N. Kim, *Tetrahedron Lett.* **2006**, *47*, 5681–5685; j) K. Fukuhara, Y. Takayama, F. Sato, *J. Am. Chem. Soc.* **2003**, *125*, 6884–6885; k) V. Gevorgyan, L. G. Quan, Y. Yamamoto, *J. Org. Chem.* **1998**, *63*, 1244–1247, and references cited therein; l) Z. Guo, A. G. Schultz, *Org. Lett.* **2001**, *8*, 1177–1180; m) T. Kondo, M. Niimi, M. Nomura, K. Wada, T.-a. Mitsudo, *Tetrahedron Lett.* **2007**, *48*, 2837–2839; n) S. Carrettin, M. C. Blanco, A. Corma, A. S. K. Hashmi, *Adv. Synth. Catal.* **2006**, *348*, 1283–1288; o) J.-z. Tian, J.-q. Zhang, X. Shen, H.-x. Zou, *J. Organomet. Chem.* **1999**, *584*, 240–245; p) D. J. Krysan, A. Gurski, L. S. Liebeskind, *J. Am. Chem. Soc.* **1992**, *114*, 1412–1418.

[13] J. W. Patterson, *J. Org. Chem.* **1995**, *60*, 560–563.

[14] R. E. Maleczka Jr, F. Shi, D. Holmes, M. R. Smith III, *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793.

[15] a) F. A. Khan, B. Rout, *Tetrahedron Lett.* **2006**, *47*, 5251–5253; b) F. A. Khan, B. Rout, *J. Org. Chem.* **2007**, *72*, 7011–7013; c) F. A. Khan, V. Dwivedi, B. Rout, *Tetrahedron Lett.* **2007**, *48*, 207–209; d) F. A. Khan, R. Satapathy, J. Dash, G. Savitha, *J. Org. Chem.* **2004**, *69*, 5295–5301; e) F. A. Khan, J. Dash, *J. Am. Chem. Soc.* **2002**, *124*, 2424–2425; f) F. A. Khan, J. Dash, Ch. Sudheer, N. Sahu, K. Parasuraman, *J. Org. Chem.* **2005**, *70*, 7565–7577; g) F. A. Khan, J. Dash, *J. Org. Chem.* **2003**, *68*, 4556–4559; h) F. A. Khan, J. Dash, N. Sahu, Ch. Sudheer, *J. Org. Chem.* **2002**, *67*, 3783–3787; i) F. A. Khan, K. S. Krishnakumar, Ch. Sudheer, *Synthesis* **2007**, *7*, 1054–1060; j) F. A. Khan, C. N. Rao, *Tetrahedron Lett.* **2006**, *47*, 7567–7670.

[16] a) F. A. Khan, J. Dash, D. Jain, B. Prabhudas, *J. Chem. Soc. Perkin Trans. 1* **2001**, 3132–3134; b) F. A. Khan, S. Choudhury, *Eur. J. Org. Chem.* **2006**, 672–676; c) F. A. Khan, S. Choudhury, *Synth. Commun.* **2006**, *36*, 3749–3760.

[17] F. A. Khan, B. Prabhudas, *Tetrahedron Lett.* **1999**, *40*, 9289–9292.

[18] P. U. Müller, E. Weber, G. Rheinwald, W. Seichter, *Org. Biomol. Chem.* **2005**, *3*, 3757–3766.

[19] T. Lu, T. Markotan, F. Coppo, B. Tomczuk, C. Crysler, S. Eisennagel, J. Spurlino, L. Gremminger, R. M. Soll, E. C. Giardino, R. Bone, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3727–3731.

[20] To examine whether the formation of the methyl ethers **11** was intermolecular or intramolecular in nature, the fragmentation reaction was carried out with substrate **7b** under optimized conditions at two different molar concentrations. It was observed that with dilution the yield of **11b** decreases (37% in 0.07 M to 19% in 0.027 M) with a consequent proportionate increase in the yield of **10b** (53% to 67%), the overall yield re-

maining almost the same. These results are clearly indicative of an intermolecular reaction mechanism.

[21] a) Decomposition of **7e** or **7f** took place in tightly stoppered RB flasks on prolonged storage at room temperature. Slow decomposition was observed from the gradual color change from white to reddish-brown, resulting in the formation of MeBr together with the usual products (i.e. **10e** and **11e**, or **10f** and **11f**). Decomposition took place even in a refrigerator (5–10 °C), but the time required was much longer; b) MeBr being a gas with a low boiling point, special precautions were taken during ^{1}H NMR sample preparation.

[22] Although compound **7b**, bearing an *n*-butyl substituent (R = *n*-C_4H_9), had been used as the model substrate for most of the experiments, substrate **7e**, with a phenyl substituent (R = Ph), was utilized in this case to avoid the overlapping of peaks in the aliphatic region in the ^{1}H NMR spectrum of the reaction mixture and in order to facilitate easy detection of the ethyl ether product.

[23] For the use of TsOMe as a methylating agent, see: a) P. Francotte, P. d. Tullio, T. Podona, O. Diouf, P. Fraikin, P. Lestage, L. Danober, J.-Y. Thomas, D.-H. Caignard, B. Pirotte, *Bioorg. Med. Chem.* **2008**, *16*, 9948–9956; b) S. Sakami, M. Maeda, K. Kawai, T. Aoki, K. Kawamura, H. Fujii, K. Hasebe, M. Nakajima, T. Endo, S. Ueno, T. Ito, J. Kamei, H. Nagase, *J. Med. Chem.* **2008**, *51*, 4404–4411.

[24] H.-J. Albert, W. P. Neumann, *Synthesis* **1980**, 942–943.

Received: January 20, 2010
Published Online: April 14, 2010

