

An Efficient Route to Pentasubstituted Phenols

Faiz Ahmed Khan^{*[a]} and Sumit Choudhury^[a]**Keywords:** Pentasubstituted phenols / Grob-type fragmentation / Cycloaddition / Rearrangement / Diels–Alder reaction

A simple and convenient three-step protocol for the synthesis of pentasubstituted tribromophenols based on the acid-catalyzed Grob-type fragmentation of the bicyclic ketone precursors **8a–e** in high overall yield is described. The bicyclic ketones **8a–e** were obtained in two steps starting from the

Diels–Alder cycloadducts **5a–e** of β -substituted vinyl acetates and tetrabromo-5,5-dimethoxycyclopentadiene.

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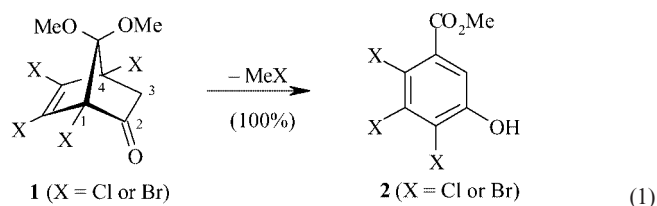
Introduction

Phenolic derivatives are ubiquitous both as naturally occurring molecules and as important industrial intermediates.^[1] Brominated phenols have been reported to occur naturally in some marine sediments. Recent studies revealed the wide occurrence of bromophenols in marine algae which are believed to be a possible source of such compounds in fish that feed predominantly on ocean plants.^[2] Interestingly a large number of brominated phenols have been detected in the blood of humans and wild animals as well as in fish and their role in living systems has been the subject of intense study.^[3]

Although substituted phenols are conventionally prepared from benzenoid precursors, numerous methods are available to construct the benzene skeleton from acyclic precursors.^[4] Substituted phenols have also been prepared from cyclic six-membered dienones by rearrangement.^[5] Ring-opening followed by rearrangement of Diels–Alder cycloadducts of substituted furans is another convenient route to phenol derivatives.^[6] Photochemical rearrangement of bicyclo[3.1.0]hex-3-en-2-ones has been reported to lead to substituted phenols.^[7]

Recently we demonstrated the quantitative conversion of 1,4,5,6-tetrahalo-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2-one (**1**) to the 2,3,4-trihalophenol derivative **2** [Equation (1)].^[8] The bicyclic ketone precursor **1** was derived from the Diels–Alder cycloadduct of vinyl acetate and tetrahalo-5,5-dimethoxycyclopentadiene by hydrolysis of the initial adduct followed by oxidation.^[8] It occurred to us that a general methodology for the synthesis of alkyl- or aryl-substituted tribromophenols could be developed if we succeed in placing an alkyl or aryl substituent at the C3 atom in **1**. We herein report an efficient three-step protocol for

the synthesis of pentasubstituted phenols based on this strategy.

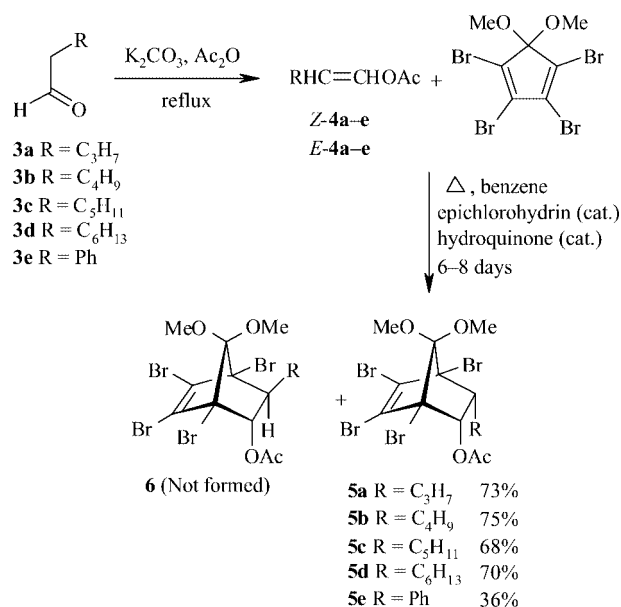


Results and Discussion

To install an alkyl or aryl group at the C3 atom of **1**, β -substituted vinyl acetates were considered as potential precursors. A literature search revealed that the use of β -substituted vinyl acetates as dienophiles in Diels–Alder reactions of tetrabromo-5,5-dimethoxycyclopentadiene remained unexplored. We thought of evaluating the efficacy of this cycloaddition reaction in order to obtain alkyl- or aryl-substituted bicyclic ketones, suitable precursors of the corresponding 2,3,4-tribromophenol derivatives. The β -substituted vinyl acetates were prepared starting from aldehydes **3a–e**, using known procedures,^[9] to give a mixture of (*Z*)- and (*E*)-**4a–e** (Scheme 1). The (*Z*)/(*E*) mixture of enol acetates **4** (taken in excess) was subjected to Diels–Alder reaction with tetrabromo-5,5-dimethoxycyclopentadiene in the presence of catalytic amounts of hydroquinone (free-radical scavenger) and epichlorohydrin (acid scavenger). The reaction required 6–8 days at 140–150 °C in a sealed tube and furnished a 68–75% yield of *endo,endo* adducts **5a–d**. For **4e** the yield was only 36% since the reaction was carried out at 120 °C owing to decomposition at higher temperature as indicated by the gradually increasing black color of the reaction mixture. Note that only the (*Z*)-enol acetates **4a–e** reacted to furnish the *endo,endo* adducts **5a–e**. The *endo,exo* adducts **6** were not formed presumably as a result of unfav-

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avorable steric interactions between the R and OMe groups of the diene in the transition state.



Scheme 1. Synthesis of *endo,endo* adducts **5a–e**.

Unambiguous structural proof for the formation of *endo,endo* adducts **5a–e** came from ¹H NMR spectroscopy (400 MHz). The coupling constants for C2-H_{exo} (H^a) with C3-H_{exo} (H^b) and C3-H_{endo} (H^c) are quite diagnostic and fall in the range of 8.0–8.3 Hz for H^{a,b} and 2.1–2.4 Hz for H^{a,c} (Figure 1). Comparison of the observed coupling constants of unsubstituted alcohols^[8] with those of **5a–e**, given in Figure 1, clearly indicates that the R group is *endo*. Another characteristic feature is the chemical shifts of the H^b and H^c protons. The *endo* proton (H^c) is shielded and appears at around 1.75 ppm. The observed chemical shift for **5a** (2.75–2.71 ppm, Figure 1) provides support for the *endo* assignment of the R group. Similarly, the C3-H chemical shifts for **5b–e** are consistent with this assignment (see Experimental Section).

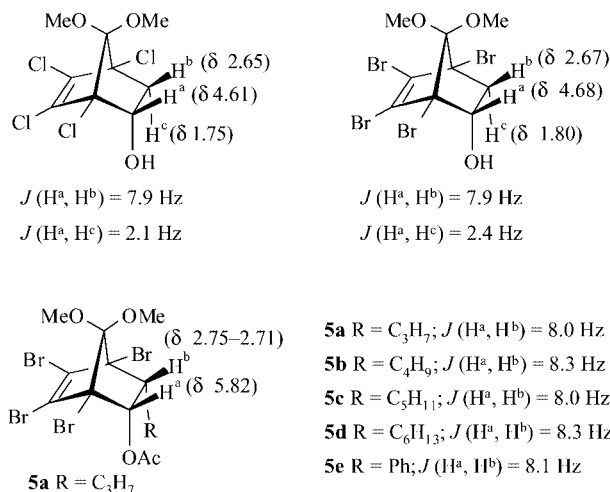
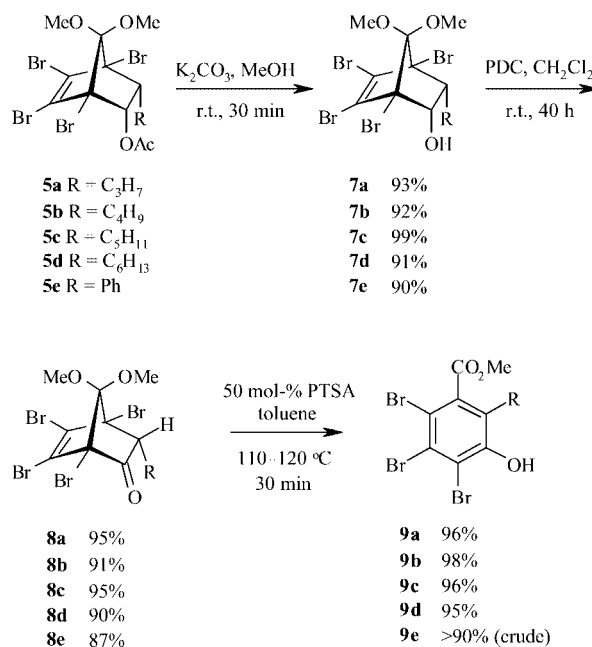


Figure 1. Comparison of the coupling constants and chemical shifts of **5a** with those of the parent alcohols.

Having obtained the requisite cycloadducts **5a–e**, our next task was to convert them efficiently to substituted bicyclic ketones and finally to the tribromophenols. This straightforward three-step sequence is depicted in Scheme 2. The cycloadducts **5a–e** were hydrolyzed employing K₂CO₃ in MeOH to furnish 90–99% yield of the alcohols **7a–e**. Oxidation of the secondary alcohol group was accomplished in excellent yield using PDC in dichloromethane at room temperature to obtain the bicyclic ketones **8a–e**.



Scheme 2. Synthesis of pentasubstituted tribromo phenols **9** from Diels–Alder adducts **5**.

For the final step, which involved Grob-type fragmentation of the C1–C7 bond, the reaction conditions were optimized using bicyclic ketone **8c**. Unlike the parent bicyclic ketone **1**, which underwent smooth fragmentation at room temperature on standing and spontaneous cleavage at 90 °C,^[8] the substituted **8c** remained unchanged even after heating in DMSO at 100 °C for two hours. The results of optimization are shown in Table 1. When 50 mol-% of the acid catalyst (PTSA) was used in DMSO, no change was observed at room temperature nor at 130 °C (entries 2 and 3, Table 1). When the temperature was elevated to 150 °C, the product **9c** was formed in 86% yield. Toluene appeared to be the solvent of choice, furnishing a near quantitative yield of **9c** in just 30 minutes with both 100 and 50 mol-% of acid catalyst (entries 5 and 6, Table 1). Reducing the amount of acid catalyst to 20 mol-% showed no beneficial effects. Therefore, the conditions given in entry 6 of Table 1 (50 mol-% PTSA, 110–120 °C, toluene) were used for the reactions of the ketones **8a–e**.

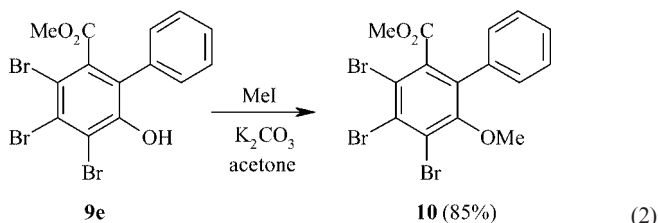
The fragmentation product **9e**, derived from bicyclic ketone **8e**, was converted into the corresponding methyl ether **10** by treatment with MeI/K₂CO₃ [Equation (2)]. This was done for the sake of purification and characterization

Table 1. Grob-type fragmentation of **8c** to give **9c**.

Entry	Solvent	Temp. [°C]	Catalyst [mol-%]	Time	Product yield ^[a] [%]
1	DMSO	100	–	2 h	no reaction
2	DMSO	room temp.	PTSA (50)	2 h	no reaction
3	DMSO	130	PTSA (50)	1 h	no reaction
4	DMSO	150	PTSA (50)	6 h	86
5	toluene	110–120	PTSA (100)	30 min	97
6	toluene	110–120	PTSA (50)	30 min	96
7	toluene	110–120	PTSA (20)	12 h	slow reaction ^[b]

[a] Isolated yield. [b] Little product was formed; unreacted starting material was the major component, as monitored by TLC.

since the polarity of **9e** was such that it could not be cleanly separated from impurities.



We have established a simple and convenient three-step protocol for the synthesis of pentasubstituted tribromophenols based on a Grob-type fragmentation strategy. The bicyclic ketone precursors **8a–e** were acquired in high overall yield from the Diels–Alder cycloadducts **5a–e**, formed from β -substituted vinyl acetates and tetrabromo-5,5-dimethoxycyclopentadiene, by hydrolysis followed by efficient oxidation of the resulting secondary alcohols **7a–e**. Both alkyl as well as aryl substituents work equally well. The Grob-type fragmentation of bicyclic ketone precursors **8a–e** was triggered in the presence of acid catalyst PTSA to furnish near quantitative yields of the pentasubstituted tribromophenols **9a–e**.

Experimental Section

General Information: Melting points are uncorrected. IR spectra were recorded in the form of KBr pellets (solids) or as thin films (liquids). ¹H NMR and proton decoupled ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively. NMR data are reported as follows: multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], coupling constant(s) in Hz, integration, assignment. Samples for NMR analysis were prepared in CDCl₃ and tetramethylsilane was used as the internal standard. Column chromatography was performed using silica gel (Acme: 100–200 mesh) with ethyl acetate/hexane used as eluent. The mixtures of enol acetates, (Z)/(E)-**4a**,^[10a] **4b**,^[10b,10c] **4c**,^[10d] **4d**^[10e] and **4e**,^[10b,10e] were prepared according to the literature procedure.^[9]

General Procedure for the Preparation of Diels–Alder Adducts 5a–e: A mixture of tetrabromo-5,5-dimethoxycyclopentadiene (3.016 g, 6.82 mmol), excess enol acetate (Z)/(E)-**4a** [9 mL; (Z)/(E) $\approx$ 38:62], catalytic amounts of hydroquinone (5 mg) and epichlorohydrin (0.5 mL) in dry benzene (10 mL) was heated at 140–150 °C in a sealed tube under an inert atmosphere for 6–8 days. The solvent was evaporated under reduced pressure. The reaction mixture was then distilled (2 mbar, 110 °C) using a kugelrohr apparatus to remove the excess enol acetate **4a** to furnish a deep-red oily mass

which was purified by chromatography on a silica gel column using ethyl acetate/hexane as the eluent to furnish the Diels–Alder cycloadduct **5a**.

1,4,5,6-Tetrabromo-3-propyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (5a): R_f = 0.70 (5% EtOAc in hexane); yield: 2.494 g, 73%; solid, m.p. 84–86 °C; unreacted diene recovered: 375 mg, 12%. ¹H NMR (400 MHz, CDCl₃): δ = 5.82 (d, J = 8.0 Hz, 1 H, C2-H_{exo}), 3.56 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 2.75–2.71 (m, 1 H, C3-H_{exo}), 2.02 (s, 3 H, -OCOCH₃), 1.51–1.46 (m, 1 H), 1.12–1.09 (several m, 3 H), 0.81 (t, J = 6.8 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 170.1, 125.8, 123.4, 111.3, 78.5, 73.2, 71.5, 53.1, 52.3, 51.7, 26.1, 21.5, 20.5, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1720, 1560, 1420, 1350, 1200, 1160, 1120, 1080, 1040 cm^{–1}.

1,4,5,6-Tetrabromo-3-butyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (5b): R_f = 0.70 (5% EtOAc in hexane); yield: 2.976 g, 75% from tetrabromo-5,5-dimethoxycyclopentadiene (3.012 g, 6.82 mmol) and enol acetate (Z)/(E)-**4b** [9 mL; (Z)/(E) $\approx$ 36:64]; solid, m.p. 110 °C. ¹H NMR (400 MHz, CDCl₃): δ = 5.89 (d, J = 8.3 Hz, 1 H, C2-H_{exo}), 3.63 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 2.77–2.76 (m, 1 H, C3-H_{exo}), 2.09 (s, 3 H, -OCOCH₃), 1.57–1.55 (m, 2 H), 1.32–1.07 (several m, 4 H), 0.86 (t, J = 7.1 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 170.1, 125.8, 123.4, 111.3, 78.5, 73.2, 71.5, 52.5, 52.1, 51.8, 30.4, 23.6, 22.7, 20.5, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1740, 1560, 1420, 1360, 1280, 1200 cm^{–1}. C₁₅H₂₀O₄Br₄ (583.94): calcd. C 30.85, H 3.45; found C 31.01, H 3.68.

1,4,5,6-Tetrabromo-3-pentyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (5c): R_f = 0.70 (5% EtOAc in hexane); yield: 1.176 g, 68% from tetrabromo-5,5-dimethoxycyclopentadiene (1.278 g, 2.89 mmol) and enol acetate (Z)/(E)-**4c** [3.6 mL; (Z)/(E) $\approx$ 35:65]; viscous liquid. ¹H NMR (400 MHz, CDCl₃): δ = 5.82 (d, J = 8.0 Hz, 1 H, C2-H_{exo}), 3.56 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 2.73–2.68 (m, 1 H, C3-H_{exo}), 2.02 (s, 3 H, -OCOCH₃), 1.5–1.45 (m, 1 H), 1.21–1.04 (m, 7 H), 0.80 (t, J = 6.8 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 169.9, 125.7, 123.3, 111.2, 78.4, 73.1, 71.4, 53.0, 52.4, 51.7, 31.8, 27.9, 23.9, 22.3, 20.4, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1740, 1540, 1440, 1360, 1180 cm^{–1}.

1,4,5,6-Tetrabromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl Acetate (5d): R_f = 0.70 (5% EtOAc in hexane); yield: 2.702 g, 70% from tetrabromo-5,5-dimethoxycyclopentadiene (2.797 g, 6.33 mmol) and enol acetate (Z)/(E)-**4d** [9 mL; (Z)/(E) $\approx$ 32:68]; viscous liquid. ¹H NMR (400 MHz, CDCl₃): δ = 5.88 (d, J = 8.3 Hz, 1 H, C2-H_{exo}), 3.63 (s, 3 H, OMe), 3.58 (s, 3 H, OMe), 2.79–2.75 (m, 1 H, C3-H_{exo}), 2.09 (s, 3 H, -OCOCH₃), 1.57–1.53 (m, 1 H), 1.28–1.11 (several m, 9 H), 0.87 (t, J = 6.8 Hz, 3 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 169.9, 125.7, 123.3, 111.2, 78.4, 73.1, 71.4, 53.0, 52.4, 51.6, 31.5, 29.3, 28.2, 23.9, 22.5, 20.4, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2900, 1760, 1580, 1460, 1360, 1220, 1180 cm^{–1}.

1,4,5,6-Tetrabromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-yl Acetate (5e): $R_f = 0.70$ (10% EtOAc in hexane); yield: 0.768 g, 36% from tetrabromo-5,5-dimethoxycyclopentadiene (2.035 g, 4.60 mmol) and enol acetate (*Z*)/(*E*)-**4e** [1.4 mL; (*Z*)/(*E*) $\approx$ 35:65]; unreacted diene recovered: 463 mg, 23%; solid, m.p. 134 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.29\text{--}7.26$ (m, 3 H), 7.12–7.09 (m, 2 H), 5.8 (d, $J = 8.1$ Hz, 1 H, C2-H_{exo}), 4.07 (d, $J = 8.0$ Hz, 1 H, C3-H_{exo}), 3.72 (s, 3 H, OMe), 3.63 (s, 3 H, OMe), 1.83 (s, 3 H, $-\text{OCOCH}_3$) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 169.5$, 131.8, 131.4, 128.2, 127.7, 127.3, 124.2, 111.9, 81.1, 73.6, 70.9, 58.6, 53.3, 51.9, 20.4 ppm. IR (KBr): $\tilde{\nu} = 2900$, 1740, 1560, 1480, 1440, 1360, 1220, 1180, 1060, 980, 860 cm^{-1} . $\text{C}_{17}\text{H}_{16}\text{Br}_4\text{O}_4$ (603.93): calcd. C 33.77, H 2.65; found C 33.85, H 2.54.

General Procedure for the Preparation of Alcohols 7a–e: K_2CO_3 (460 mg, 3.33 mmol) was added to a solution of the cycloadduct **5a** (1.637 g, 3.22 mmol) in MeOH (15 mL) and the mixture was stirred at room temperature for 30 min. After complete consumption of the starting material (TLC monitoring) the solvent was evaporated under reduced pressure, water (20 mL) was added to the residue and the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were then washed with brine and dried with anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel using ethyl acetate/hexane as the eluent to afford the alcohol **7a**.

1,4,5,6-Tetrabromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-ol (7a): $R_f = 0.60$ (5% EtOAc in hexane); yield: 1.583 g, 93%; solid, m.p. 110–112 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 4.64$ (d, $J = 8.0$ Hz, 1 H, C2-H_{exo}), 3.58 (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 2.66–2.61 (m, 1 H, C3-H_{exo}), 1.86 (br. s, 1 H, D_2O exchangeable), 1.53–1.44 (m, 2 H), 1.35–1.24 (m, 2 H), 0.91 (t, $J = 6.8$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 125.9$, 122.7, 111.4, 79.6, 74.8, 73.8, 53.0, 52.4, 51.6, 25.9, 22.4, 14.2 ppm. IR (KBr): $\tilde{\nu} = 3500$ (OH), 2900, 1550, 1440, 1240, 1160, 1140, 1080, 1040, 960 cm^{-1} .

1,4,5,6-Tetrabromo-3-butyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (7b): $R_f = 0.60$ (5% EtOAc in hexane); yield: 2.470 g, 92% from **5b** (2.902 g, 4.96 mmol); solid, m.p. 76–78 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 4.59$ (d, $J = 7.8$ Hz, 1 H, C2-H_{exo}), 3.53 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 2.59–2.55 (m, 1 H, C3-H_{exo}), 1.77 (br. s, 1 H, D_2O exchangeable), 1.50–1.20 (several m, 6 H), 0.83 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 125.9$, 122.7, 111.3, 79.6, 74.7, 73.8, 53.0, 52.5, 51.6, 31.4, 23.4, 22.7, 13.9 ppm. IR (KBr): $\tilde{\nu} = 3450$ (OH), 2900, 1560, 1440, 1160, 1140, 1060, 1000, 960 cm^{-1} . $\text{C}_{13}\text{H}_{18}\text{Br}_4\text{O}_3$ (541.90): calcd. C 28.81, H 3.35; found C 29.07, H 3.52.

1,4,5,6-Tetrabromo-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-ol (7c): $R_f = 0.60$ (5% EtOAc in hexane); yield: 979 mg, 99% from **5c** (1.058 g, 1.77 mmol); viscous liquid. ^1H NMR (400 MHz, CDCl_3): $\delta = 4.68$ (d, $J = 8.0$ Hz, 1 H, C2-H_{exo}), 3.60 (s, 3 H, OMe), 3.57 (s, 3 H, OMe), 2.67–2.62 (m, 1 H, C3-H_{exo}), 1.95 (br. s, 1 H, D_2O exchangeable), 1.66–1.43 (m, 2 H), 1.37–1.26 (m, 6 H), 0.88 (t, $J = 6.8$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 125.9$, 122.7, 111.3, 79.5, 74.7, 73.8, 52.9, 52.6, 51.5, 31.8, 28.9, 23.7, 22.5, 14.0 ppm. IR (neat): $\tilde{\nu} = 3400$, 2900, 1560, 1440, 1180, 1140 cm^{-1} .

1,4,5,6-Tetrabromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-ol (7d): $R_f = 0.60$ (5% EtOAc in hexane); yield: 2.262 g, 91% from **5d** (2.663 g, 4.35 mmol); viscous liquid. ^1H NMR (400 MHz, CDCl_3): $\delta = 4.59$ (d, $J = 8.1$ Hz, 1 H, C2-H_{exo}), 3.53 (s, 3 H, OMe), 3.51 (s, 3 H, OMe), 2.60–2.55 (m, 1 H, C3-H_{exo}), 1.84 (br. s, 1 H, D_2O exchangeable), 1.52–1.47 (m, 1 H), 1.41–1.37 (m, 1 H), 1.29–1.27 (m, 1 H), 1.24–1.21 (m, 7 H), 0.81 (t, $J = 6.8$ Hz, 3 H) ppm.

^{13}C NMR (100 MHz, CDCl_3): $\delta = 125.9$, 122.7, 111.4, 79.6, 74.8, 73.8, 53.0, 52.6, 51.6, 31.7, 29.4, 29.2, 23.8, 22.6, 14.1 ppm. IR (neat): $\tilde{\nu} = 3500$ (OH), 2900, 1560, 1460, 1180, 1160, 1100, 960 cm^{-1} .

1,4,5,6-Tetrabromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-ol (7e): $R_f = 0.50$ (10% EtOAc in hexane); yield: 576 mg, 90% from **5e** (683 mg, 1.13 mmol); solid, m.p. 106 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 7.34\text{--}7.29$ (m, 3 H), 7.25–7.21 (m, 2 H), 4.84 (d, $J = 7.8$ Hz, 1 H, C2-H_{exo}), 3.89 (d, $J = 8.0$ Hz, 1 H, C3-H_{exo}), 3.69 (s, 3 H, OMe), 3.62 (s, 3 H, OMe), 1.97 (br. s, 1 H, D_2O exchangeable) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 132.4$, 131.4, 128.2, 127.8, 126.6, 124.3, 111.7, 80.6, 74.3, 74.1, 58.8, 53.3, 51.8 ppm. IR (KBr): $\tilde{\nu} = 3500$, 2900, 1560, 1490, 1440, 1400, 1180, 1100, 1020, 960, 880, 800 cm^{-1} . $\text{C}_{15}\text{H}_{14}\text{Br}_4\text{O}_3$ (561.89): calcd. C 32.03, H 2.49; found C 31.89, H 2.16.

General Procedure for the Preparation of Bicyclic Ketones 8a–e: CrO_3 (1.669 g, 16.69 mmol) was added to a solution of pyridine (2.637 g, 33.38 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred at room temperature for 30 min. A solution of the alcohol **7a** (1.307 g, 2.475 mmol) in CH_2Cl_2 (50 mL) was added to this deep brown colored mixture and the mixture was stirred at room temperature for 40 h. The inorganic solids were then filtered off through a small silica gel pad and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to furnish the corresponding bicyclic ketone **8a**.

1,4,5,6-Tetrabromo-7,7-dimethoxy-3-propylbicyclo[2.2.1]hept-5-en-2-one (8a): $R_f = 0.80$ (5% EtOAc in hexane); 1.237 g, 95%; solid, m.p. 82–84 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 3.63$ (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 2.68 (dd, $J = 4.8$, 8.4 Hz, 1 H, C3-H_{exo}), 1.72–1.38 (several m, 4 H), 0.92 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 196.7$, 130.9, 118.9, 114.4, 78.5, 70.7, 53.4, 51.8, 51.9, 29.9, 21.4, 13.9 ppm. IR (KBr): $\tilde{\nu} = 2900$, 1750 (C=O), 1550, 1440, 1160, 1100, 960 cm^{-1} .

1,4,5,6-Tetrabromo-3-butyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (8b): $R_f = 0.80$ (5% EtOAc in hexane); yield: 1.825 g, 91% from **7b** (2.012 g, 3.7 mmol); solid, m.p. 76 °C. ^1H NMR (400 MHz, CDCl_3): $\delta = 3.62$ (s, 3 H, OMe), 3.59 (s, 3 H, OMe), 2.67 (dd, $J = 4.5$, 8.2 Hz, 1 H, C3-H_{exo}), 1.72–1.27 (several m, 6 H), 0.89 (t, $J = 7.3$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 196.7$, 130.9, 118.9, 114.4, 78.5, 70.8, 53.4, 52.1, 51.9, 30.2, 27.6, 22.5, 13.8 ppm. IR (KBr): $\tilde{\nu} = 2900$, 1760 (C=O), 1560, 1480, 1200, 1140, 1120, 980, 880 cm^{-1} . $\text{C}_{13}\text{H}_{16}\text{O}_3\text{Br}_4$ (539.88): calcd. C 28.92, H 2.99; found C 29.07, H 3.15.

1,4,5,6-Tetrabromo-7,7-dimethoxy-3-pentylbicyclo[2.2.1]hept-5-en-2-one (8c): $R_f = 0.80$ (5% EtOAc in hexane); yield: 730 mg, 95% from **7c** (765 mg, 1.376 mmol); viscous liquid. ^1H NMR (400 MHz, CDCl_3): $\delta = 3.58$ (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 2.63 (dd, $J = 4.9$, 8.5 Hz, 1 H, C3-H_{exo}), 1.67–1.49 (m, 1 H), 1.41–1.19 (several m, 7 H), 0.83 (t, $J = 7.0$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 196.6$, 130.9, 118.9, 114.4, 78.5, 70.8, 53.4, 52.1, 51.9, 31.5, 27.9, 27.8, 22.3, 13.9 ppm. IR (neat): $\tilde{\nu} = 2900$, 1760, 1550, 1440, 1160, 1100, 960, 860 cm^{-1} .

1,4,5,6-Tetrabromo-3-hexyl-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one (8d): $R_f = 0.80$ (5% EtOAc in hexane); yield: 1.932 g, 90% from **7d** (2.161 g, 3.80 mmol); viscous liquid. ^1H NMR (400 MHz, CDCl_3): $\delta = 3.58$ (s, 3 H, OMe), 3.55 (s, 3 H, OMe), 2.63 (dd, $J = 4.8$, 8.4 Hz, 1 H, C3-H_{exo}), 1.63–1.22 (several m, 10 H), 0.82 (t, $J = 6.7$ Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 196.7$, 130.9, 118.9, 114.4, 78.5, 70.8, 53.4, 52.1, 51.9, 31.5, 29.0, 28.1, 27.9, 22.5, 14.0 ppm. IR (neat): $\tilde{\nu} = 2900$, 1760 (C=O), 1560, 1440, 1180, 960, 860 cm^{-1} .

1,4,5,6-Tetrabromo-7,7-dimethoxy-3-phenylbicyclo[2.2.1]hept-5-en-2-one (8e): R_f = 0.80 (10% EtOAc in hexane); yield: 284 mg, 87% from **7e** (327 mg, 0.582 mmol); solid, m.p. 147–148 °C. ^1H NMR (400 MHz, CDCl_3): δ = 7.27–7.24 (m, 3 H), 6.92–6.90 (m, 2 H), 4.0 (s, 1 H, C3-H_{exo}), 3.66 (s, 3 H, OMe), 3.64 (s, 3 H, OMe) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 194.5, 131.9, 131.8, 130.0, 128.5, 128.4, 118.3, 113.9, 78.9, 71.9, 57.6, 53.6, 52.2 ppm. IR (KBr): $\tilde{\nu}$ = 2900, 1750 (C=O), 1550, 1480, 1440, 1170, 1100, 960, 860 cm^{-1} .

General Procedure for the Preparation of Pentasubstituted Tribromophenols 9a–e: *p*-Toluenesulfonic acid monohydrate, PTSA (284 mg, 1.49 mmol), was added to a solution of the bicyclic ketone **8a** (1.565 g, 2.97 mmol) in toluene (10 mL) and the reaction mixture was refluxed at 110–120 °C for 30 min. After the reaction was complete (TLC monitoring), the reaction mixture was diluted with water (10 mL) and the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4 . The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography to afford the phenol derivative **9a**.

Methyl 2,3,4-Tribromo-5-hydroxy-6-propylbenzoate (9a): R_f = 0.70 (5% EtOAc in hexane); yield: 1.234 g, 96%; solid, m.p. 118–120 °C. ^1H NMR (400 MHz, CDCl_3): δ = 5.83 (br. s, 1 H, D_2O exchangeable), 3.92 (s, 3 H, OMe), 2.51 (t, J = 7.9 Hz, 2 H), 1.60–1.53 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 167.3, 150.9, 137.7, 127.7, 124.8, 115.3, 112.3, 52.8, 31.6, 22.5, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 3300 (OH), 2900, 1700 (C=O), 1540, 1400, 1360, 1260, 1220, 1160, 1120, 1060 cm^{-1} .

Methyl 2,3,4-Tribromo-6-butyl-5-hydroxybenzoate (9b): R_f = 0.70 (5% EtOAc in hexane); yield: 1.058 g, 98% from **8b** (1.303 g, 2.40 mmol); solid, m.p. 82 °C. ^1H NMR (400 MHz, CDCl_3): δ = 5.81 (br. s, 1 H, D_2O exchangeable), 3.92 (s, 3 H, -COOMe), 2.53 (t, J = 7.5 Hz, 2 H), 1.54–1.47 (m, 2 H), 1.36–1.31 (m, 2 H), 0.87 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 167.3, 150.8, 137.6, 127.9, 124.7, 115.3, 112.3, 52.8, 31.3, 29.3, 22.8, 13.7 ppm. IR (KBr): $\tilde{\nu}$ = 3200 (OH), 2900, 1700 (C=O), 1540, 1450, 1430, 1410, 1380, 1280, 1210, 1170, 1040, 980 cm^{-1} . $\text{C}_{12}\text{H}_{13}\text{Br}_3\text{O}_3$ (444.95): calcd. C 32.39, H 2.95; found C 32.19, H 3.09.

Methyl 2,3,4-Tribromo-5-hydroxy-6-pentylbenzoate (9c): R_f = 0.70 (5% EtOAc in hexane); yield: 556 mg, 96% from **8c** (700 mg, 1.263 mmol); solid, m.p. 92–94 °C. ^1H NMR (400 MHz, CDCl_3): δ = 5.75 (br. s, 1 H, D_2O exchangeable), 3.87 (s, 3 H, OMe), 2.48 (t, J = 8.1 Hz, 2 H), 1.49–1.23 (several m, 6 H), 0.82 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 167.3, 150.8, 137.6, 127.9, 124.7, 115.3, 112.3, 52.8, 31.9, 29.6, 28.9, 22.3, 13.9 ppm. IR (KBr): $\tilde{\nu}$ = 3200 (OH), 2900, 1700 (C=O), 1540, 1420, 1400, 1360, 1280, 1200, 1140, 1080 cm^{-1} .

Methyl 2,3,4-Tribromo-6-hexyl-5-hydroxybenzoate (9d): R_f = 0.70 (5% EtOAc in hexane); yield: 1.434 g, 95% from **8d** (1.812 g, 3.19 mmol); viscous liquid. ^1H NMR (400 MHz, CDCl_3): δ = 5.77 (br. s, 1 H, D_2O exchangeable), 3.87 (s, 3 H, OMe), 2.48 (t, J = 8.0 Hz, 2 H), 1.51–1.43 (m, 2 H), 1.28–1.19 (m, 6 H), 0.81 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 167.3, 150.8, 137.6, 127.9, 124.7, 115.3, 112.3, 52.8, 31.4, 29.6, 29.4, 29.1, 22.5, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 3400 (OH), 2980, 1710 (C=O), 1530, 1420, 1400, 1360, 1260, 1200, 1140, 1080, 1000, 920 cm^{-1} .

Methyl 2,3,4-Tribromo-5-methoxy-6-phenylbenzoate (10): The reaction was carried out as described in the general procedure and then the crude **9e** [$>90\%$, from **8e** (24 mg, 0.043 mmol)] was directly

converted into the corresponding methyl ether for characterization purposes as follows. Crude **9e** was dissolved in dry acetone (1.5 mL) and anhydrous K_2CO_3 (9 mg, 0.068 mmol) followed by MeI (13 mg, 0.094 mmol) were added to this solution. The reaction mixture was then stirred at room temperature for 4 h. After the reaction was complete, the reaction mixture was diluted with water (2 mL) and the aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with brine and dried with anhydrous Na_2SO_4 . The solvent was concentrated in vacuo to furnish a residue which was purified by silica gel column chromatography using ethyl acetate/hexane as the eluent to afford the methyl ether **10** (17 mg, 85%, for two steps) as a white crystalline solid, m.p. 130–132 °C, R_f = 0.80 (10% EtOAc in hexane). ^1H NMR (400 MHz, CDCl_3): δ = 7.39–7.24 (m, 5 H), 3.55 (s, 3 H, OMe), 3.37 (s, 3 H, -OMe) ppm. ^{13}C NMR (100 MHz, CDCl_3): δ = 166.6, 155.2, 137.9, 134.4, 133.8, 129.2, 128.6, 128.5, 128.2, 123.9, 117.3, 60.7, 52.6 ppm. IR (KBr): $\tilde{\nu}$ = 1720 (C=O), 1420, 1340, 1260, 1180, 1150, 1000, 960, 900, 840, 800 cm^{-1} . $\text{C}_{15}\text{H}_{11}\text{Br}_3\text{O}_3$ (478.96): calcd. C 37.58, H 2.29; found C 37.48, H 2.26.

Acknowledgments

We thank the Department of Science and Technology (DST), New Delhi for financial assistance. F. A. K. acknowledges the DST for a Swarnajayanti Fellowship. S. C. thanks the CSIR for a fellowship.

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Received: August 8, 2005

Published Online: November 30, 2005