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Polybrominated methoxy- and hydroxynaphthalenes

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Abstract: Regio- and stereoselective synthesis are described for convenient preparation of hydroxy- and methoxynaphthalenes starting from naphthalene (**1**). *cis,cis,trans*-2,3,5,8-Tetrabromo-4-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (**6**), *cis,cis,trans*-2,3,5,8-tetrabromo-1,4-dimethoxy-1,2,3,4-tetrahydronaphthalene (**7**), and *cis,cis,cis*-2,3,5,8-tetrabromo-1,4-dimethoxy-1,2,3,4-tetrahydronaphthalene (**8**) were obtained with silver-induced substitution of *trans,cis,trans*-1,2,3,4,5,8-hexabromo-1,2,3,4-tetrahydronaphthalene (**3**). Base-promoted aromatization of dimethoxides **7** and **8** afforded 3,5,8-tribromo-1-methoxynaphthalene (**9**) and 2,5,8-tribromo-1-methoxynaphthalene (**10**). The reaction of **6** with sodium methoxide formed compounds **10** and 3,5,8-tribromonaphthalen-1-ol (**16**). Bromination of **9** and **16** with Br_2 in dichloromethane at room temperature produced 2,3,5,8-tetrabromo-1-methoxynaphthalene (**14**) and 2,3,4,5,8-pentabromonaphthalen-1-ol (**18**), respectively, while compound **10** did not react in the same conditions. Pyridine-induced elimination of hexabromide **3** afforded 1,4,6-tribromnaphthalene (**21**) in 99% yield and thermolysis of the hexabromide **3** gave mainly 1,4,6,7-tetrabromonaphthalene (**22**). Tetrabromide **22** was transformed to 1,4,6,7-tetramethoxynaphthalene (**23**) by copper-assisted nucleophilic substitution reaction.

Key words: Methoxynaphthalene, silver-induced substitution, base-promoted elimination, hydroxynaphthalene, bromonaphthalene

1. Introduction

Substituted naphthalenes have gained significant industrial importance, especially in the field of pharmaceutical, optical, and electronic materials. They are useful precursors for various natural products,[1,2] e.g., their brominated analogues are admirable predecessors for the preparation of substituted naphthalenes such as phenols, amines, ethers, thioethers, epoxides, and organometallics.

Despite the considerable synthetic and biological interest in naphthalene derivatives, very few general synthetic routes are available, starting from naphthalene's core.[3] Therefore, many researchers are trying to explore the new synthetic methods for the preparation of polysubstituted naphthalenes, and the bromo naphthalenes may be the most feasible intermediates.

This paper describes mainly the preparation of new members of polysubstituted $-OCH_3$ and –OH naphthalenes from hexabrominated naphthalene **3** (prepared from **1** in two steps) by silver-induced reaction followed by a base-promoted substitution, which were further functionalized via simple bromination.

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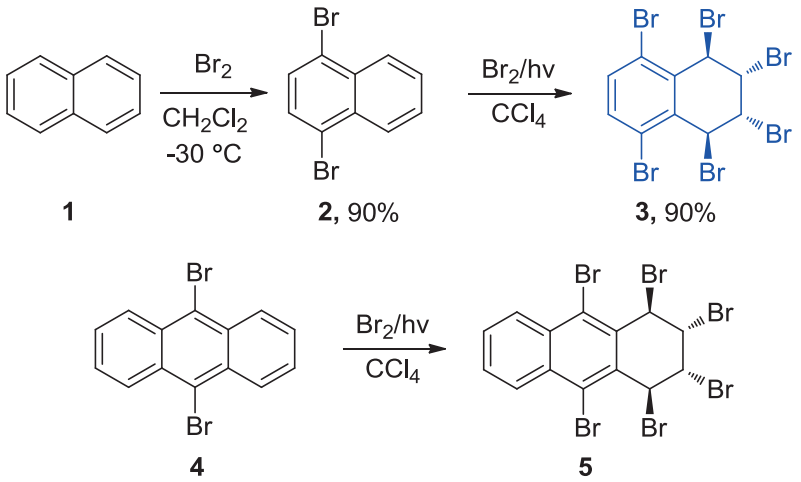
We found that hexabromide **3** is very useful intermediate for the polyfunctionalization of naphthalene and regioselective novel brominated methoxy and hydroxy derivatives of naphthalene, whose further transformation generates synthetically important novel naphthalene derivatives.

2. Results and discussion

Our recent report showed that photobromination of 9,10-dibromoanthracene (**4**) results in the formation of one stereoisomer, hexabromide **5** as the sole product,[4] while its polar bromination gave entirely different stereoisomers.[5] On the other hand, the sequential regioselective photobromination of naphthalene gave corresponding hexabromide **3** with the same stereochemistry as that of anthracene hexabromide **5** (Scheme 1).[4]



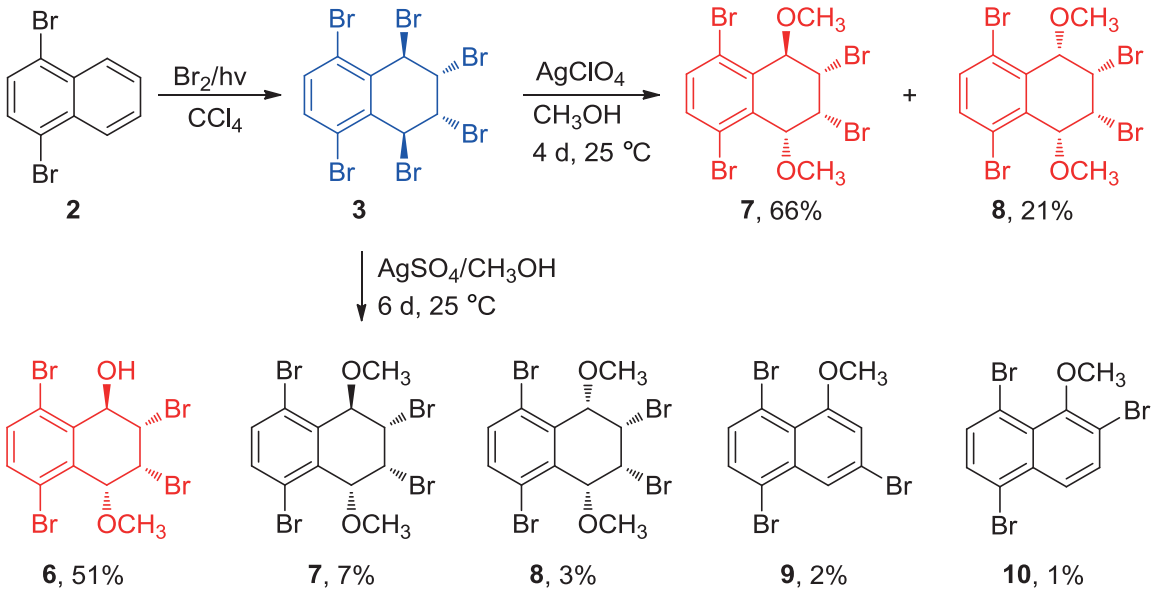
Scheme 1. Polar and photobromination of naphthalene (**1**) and 9,10-dibromoanthracene (**4**).

In this paper, we demonstrate that hexabromide **3**, which is produced by photobromination of 1,4-dibromonaphthalene (**2**)[6] is a key compound for tetralin and naphthalene derivatives.

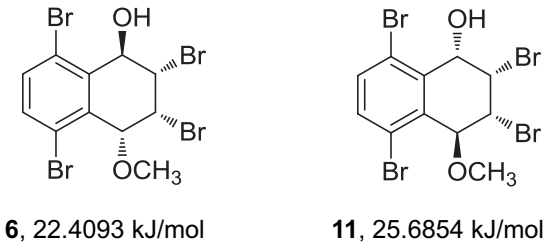
The treatment of methanolic solution of hexabromide **3** reacted with 2 equiv of $AgSO_4$ in ambient conditions for 4 days in a dark and inert atmosphere gave a mixture of brominated derivates. Careful ^{1}H NMR examination of the crude mixture revealed that exclusively derivative **6** was observed in 51% isolated yield. Furthermore, compound **6** was isolated by the crystallization of the crude mixture, while the other derivatives, compounds **7**–**10**, were separated by preparative thin layer chromatography of the residue (Scheme 2).

There was no evidence of formation of hydroxy isomer **11** in this case (Scheme 3). However, we suggest a reaction mechanism in which the stereoselective formation of compound **6** occurs by the neighboring group participation as depicted in Scheme 4. Benzylic carbocation A might be stabilized by the neighboring bromide to generate an intermediate B, which blocks the upper face of the ring and allows the methoxy group to approach from the rear face to yield stereochemically controlled species C. The second benzylic carbocation F blocked the lower face due to bromides, which may control the stereochemistry of the incoming sulfate group. The nucleophilic attack of CH_3OH at the sulfur atom of sulfate ester **G** might proceed through breakage of the S–O bond versus the C–O bond to form the corresponding alcohol **6**.

The IR spectrum of **6** displayed the absorbance signal of the hydroxy group at 3455 cm^{-1}. The appearance as a doublet at 2.86 ppm ($J_{1,OH}$ = 4 Hz) and a singlet at 3.97 ppm corresponded to hydroxy and methoxy protons, respectively. The aromatic region consisted of two doublets at 7.49 ppm and 7.55 ppm



Scheme 2. Silver induced-substitution of hexabromide **3** with Ag_2SO_4 and $AgClO_4$.

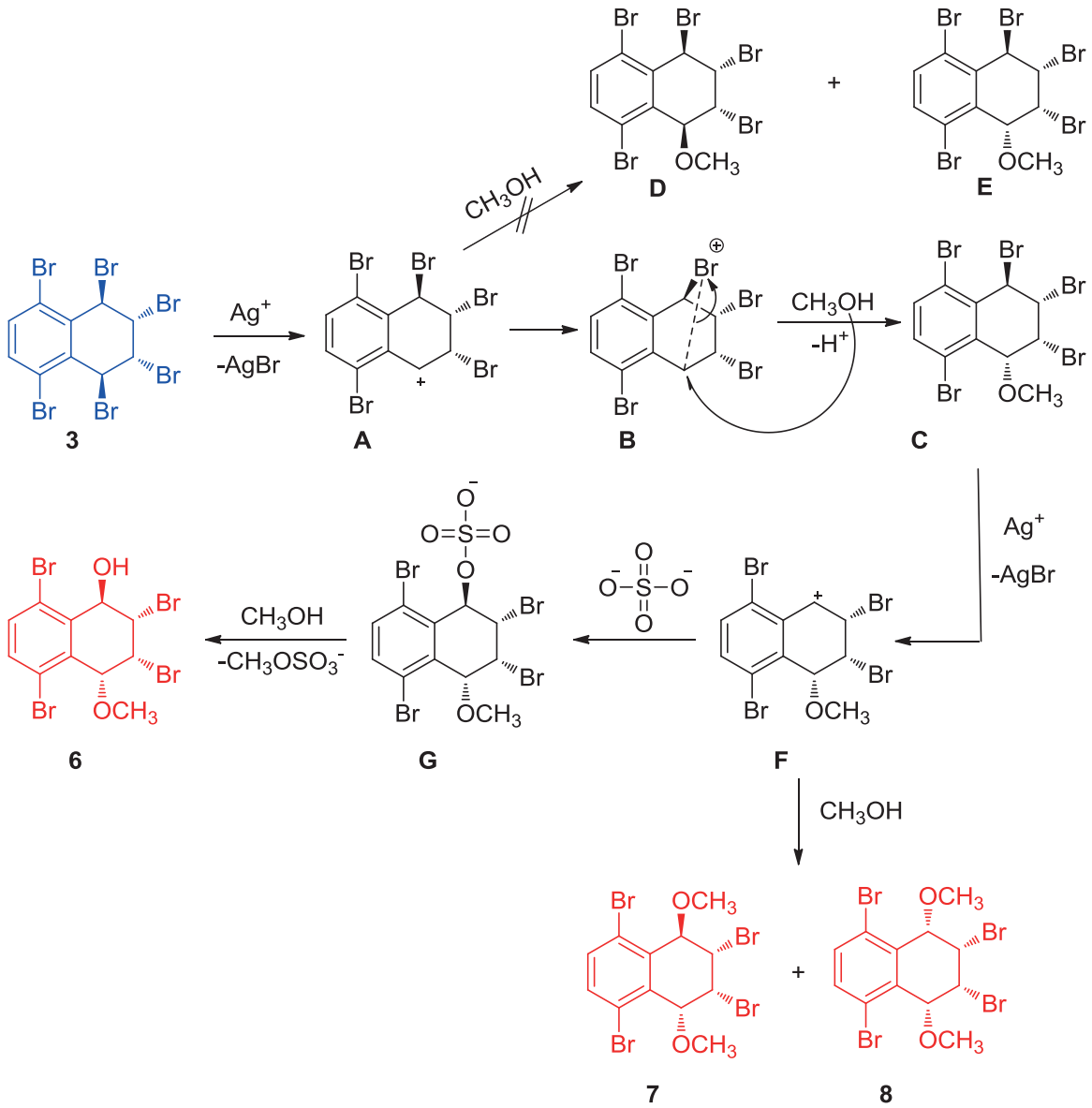


Scheme 3. Two possible isomeric structures, **6** and **11**, for hydroxymethoxide and their energy values and configurations were established by a molecular mechanics program of CS Chem Office.3

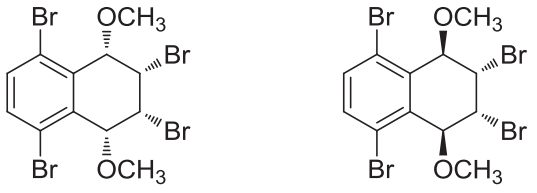
($J_{6,7}$ = 8.4 Hz), while the aliphatic part showed the existence of four protons, H_1, H_2, H_3,and H_4, at 5.48, 4.62, 5.06, and 4.72 ppm, respectively, and their coupling constants were also in agreement with their position and configuration at the ring. Ultimately, the structure and configuration were determined by X-ray crystallographic analysis. A single crystal of **6** was obtained as fawn crystals by slow evaporation from MeOH enantiomers that crystallizes in the orthorhombic enantiomorphous space group $P2_12_12_1$ with $Z = 12$ ($Z' = 3$). There are three molecules in the asymmetric unit; two of these have *(RSRR)* and the other has *(SRSS)* stereocenters (Figure).

Only one possible isomeric structure is available for unsymmetrical dimethoxide **7** in this reaction, which is further confirmed by ^{1}H NMR analysis. The splitting pattern of dimethoxy **7** consisted of six signals, two singlets and four multiplets. The singlets belonged to two methoxy protons while the multiplets at 7.52, 5.00, 4.76 and 4.74 ppm corresponded to H_{6-7}, H_4, H_1 and H_{2-3}, respectively. The ^{13}C NMR spectrum also supports the asymmetry in the molecule with the expected eleven peaks.

One aromatic singlet, one aliphatic AA′BB′ system, and one methoxy singlet in the ^{1}H NMR spectrum of **8** are in agreement with the proposed structure. Moreover, the presence of six signals in the ^{13}C NMR spectrum supports the symmetry. Two symmetrical stereoisomers, **12** and **8**, can be expected to form (Scheme 5). However, only sterically hindered and high energy dimethoxide **8** was isolated, which has four substituents on the same face of the ring system (Scheme 5).



Scheme 4. The suggested reaction mechanism for the formation of **6**, **7**, and **8**.



8, 38.5971 kJ/mol **12**, 31.1361 kJ/mol

Scheme 5. Symmetrical dimethoxides **8** and **12**.

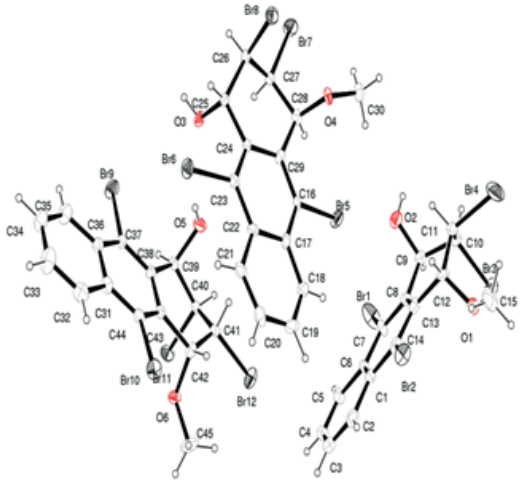
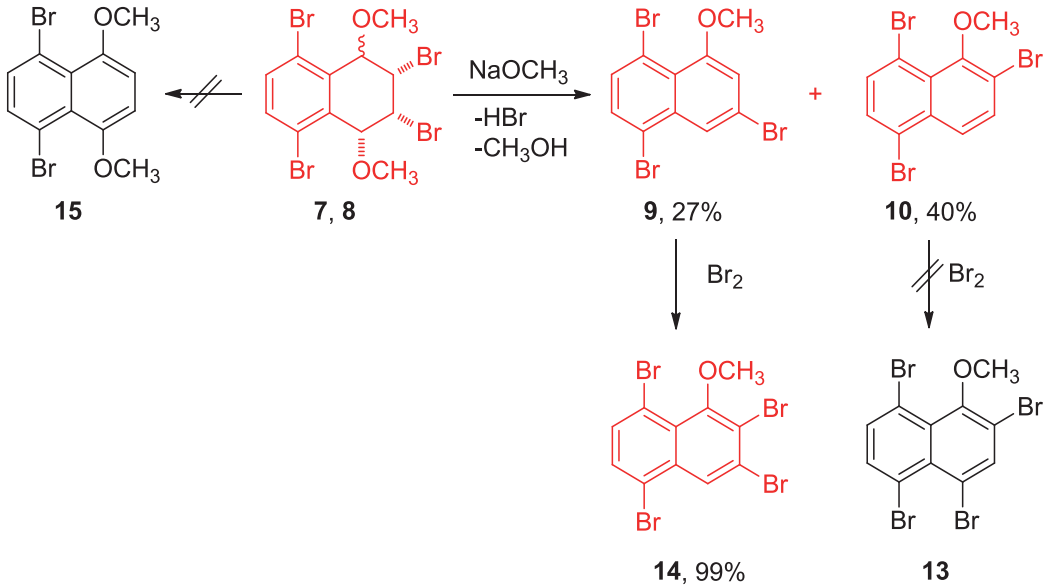


Figure. ORTEP diagram of compound **6**. Thermal ellipsoids are drawn at the 30% probability level. Stereogenic centers are as follows: C9(R), C10(S), C11(R), C12(R); C25(S), C26(R), C27(S), C28(S); C39(R), C40(S), C41(R), C42(R).

The formation of dimethoxides **7** and **8** also confirms that the reaction proceeds via carbocation intermediate **D**. Both sides of the intermediate **D** are available for incoming methoxy groups. The proposed mechanism also explains the absence of the sterically less hindered and lower energy isomer **12** (Scheme 5).

It is important to note that when the reaction was performed using $AgClO_4$ instead of Ag_2SO_4, it resulted in the formation of dimethoxy compounds **7** and **8** (Scheme 2), which were isolated in 66% and 21% yields, respectively. The difference between the two procedures can be attributed to the weak nucleophilicity of perchlorate ion as compared to sulfate ion.

After selective synthesis, successful isolation, and characterization, compounds **7** and **8** were subjected to sodium methoxide induced elimination at room temperature to afford aromatized products 1-methoxy-3-



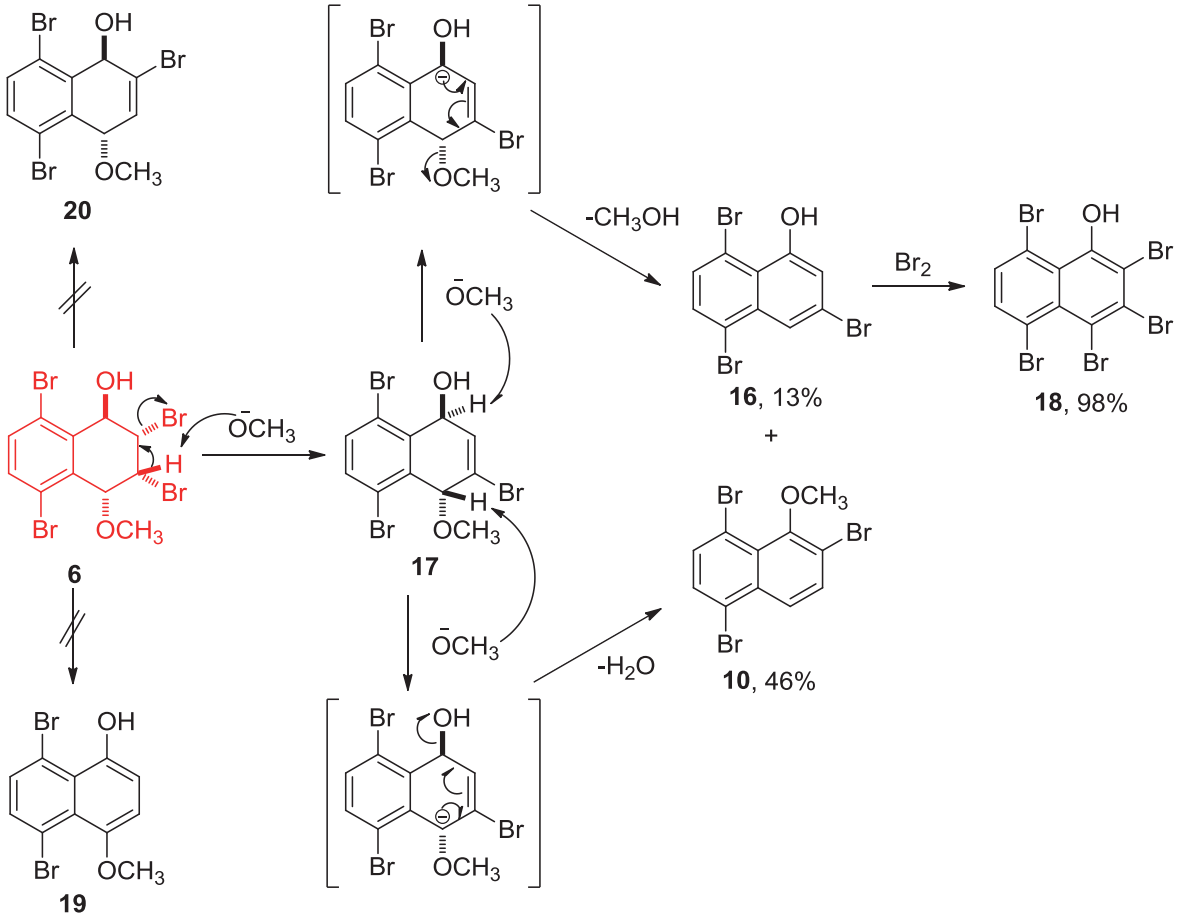
Scheme 6. Aromatization of dimethoxides **7** and **8**, followed by electrophilic bromination.

bromide (**9**) and 1-methoxy-2-bromide (**10**), which were further separated by column chromatography (Scheme 6). The ^{1}H NMR spectra of **9** and **10** exhibited the expected aromatic coupling pattern (consisting of five signal groups), an AB system ($J_{3,4}$ = 8 Hz) between H_3 and H_4 in compound **10**, and the meta coupling of H_2 and H_4 in compound **9** ($J_{2,4}$ = 2 Hz).

Therefore, for further functionalization, electrophilic bromination of compounds **9** and **10** was investigated in the dark, at room temperature, with molecular bromine. The reaction of **10** with bromine did not produce the 4-bromo product **13** under any conditions probably due to the γ-gauche effect. However, bromination of **9** with one equivalent of molecular bromine smoothly proceeded and 2,3,5,8-tetrabromo-1-methoxynaphthalene (**14**) was obtained in a quantitative yield (Scheme 6). Compound **9** was treated with excess (four equiv) bromine, but the reaction did not provide the 4-bromo product either.

One aromatic singlet, one aromatic AB system and one methoxy singlet in the ^{1}H NMR spectrum of **14** are in agreement with the proposed structure.

In order to introduce aromatization in compound **6**, the same experiment was repeated as depicted in Scheme 7. Surprisingly, no aromatized product **19** was observed in this case. Instead, 1-methoxy-2-bromide (**10**) and 1-hydroxy-3-bromide (**16**) were isolated in yields of 46% and 13%, respectively (Scheme 7). The product outcome of this reaction shows that the reaction proceeds through a selective intermediate **17** as shown in Scheme 7.

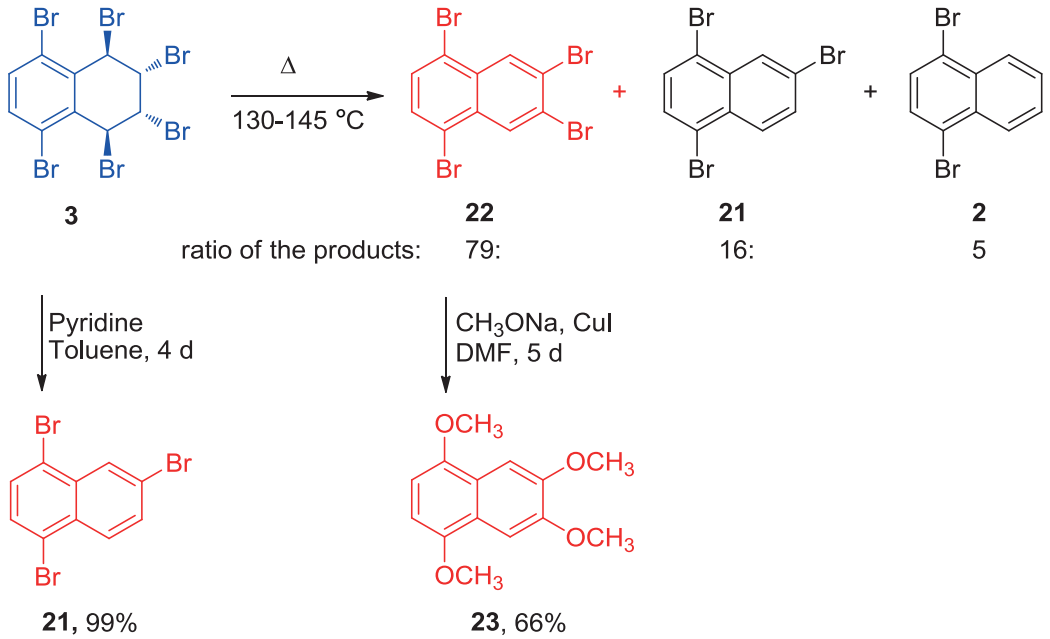


Scheme 7.

The structure of product **16** was elucidated by NMR and IR spectra. The stretching vibration band at 3401 cm^{-1} in the IR spectrum suggests the presence of a hydroxyl group. The hydroxyl proton appeared as a singlet at δ 8.22 and δ 153.6 in the ^{1}H and ^{13}C NMR spectra, which is typical aromatic carbon atom resonance bonded to hydroxyl. In addition, H_2 and H_4 appeared as doublets at δ 7.29 and δ 8.10 and their meta coupling constant $J_{2,4}$= 2 Hz confirms that Br is flanked between these two protons. The upfield shifting of H_4 is due to the electron donating mesomeric effect of the –OH group, while downfield shifting of H_2 is attributed to the van der Waals interaction of (C_5–Br)–H_4 and (C_3–Br)–H_4.

For further functionalization, electrophilic bromination of compounds **16** was also investigated in the dark, at room temperature, with excess bromine to give 2,3,4,5,8-pentabromonaphthalen-1-ol (**18**) in 98% yield (Scheme 7). The ^{1}H NMR spectrum of pentabromide **18** consists of one AB system for H_5 and H_6 and one hydroxy singlet. Nine peaks (ten peaks are expected, only nine were observed due to overlap at the aromatic region) in the ^{13}C NMR spectrum are also in accord with the proposed structure of 2,3,4,5,8-pentabromonaphthalen-1-ol (**18**).

Treatment of hexabromide **3** with pyridine afforded tribromide **21** in high yield as the sole product, while thermolysis of hexabromide **3** gave tetrabromide **22**, besides tribromide **21** and 1,4-dibromide **2** in a ratio of 79:16:5 (^{1}H NMR) (Scheme 8). After repeated crystallization, tetrabromide **22** was obtained in 69% yield. Daştan et al. also obtained the mixture of tribromide **21** and tetrabromide **22** (isolated yields: 37% and 55%, respectively) by base-promoted elimination of other stereoisomeric hexabromides or hexabromide mixtures.[7]

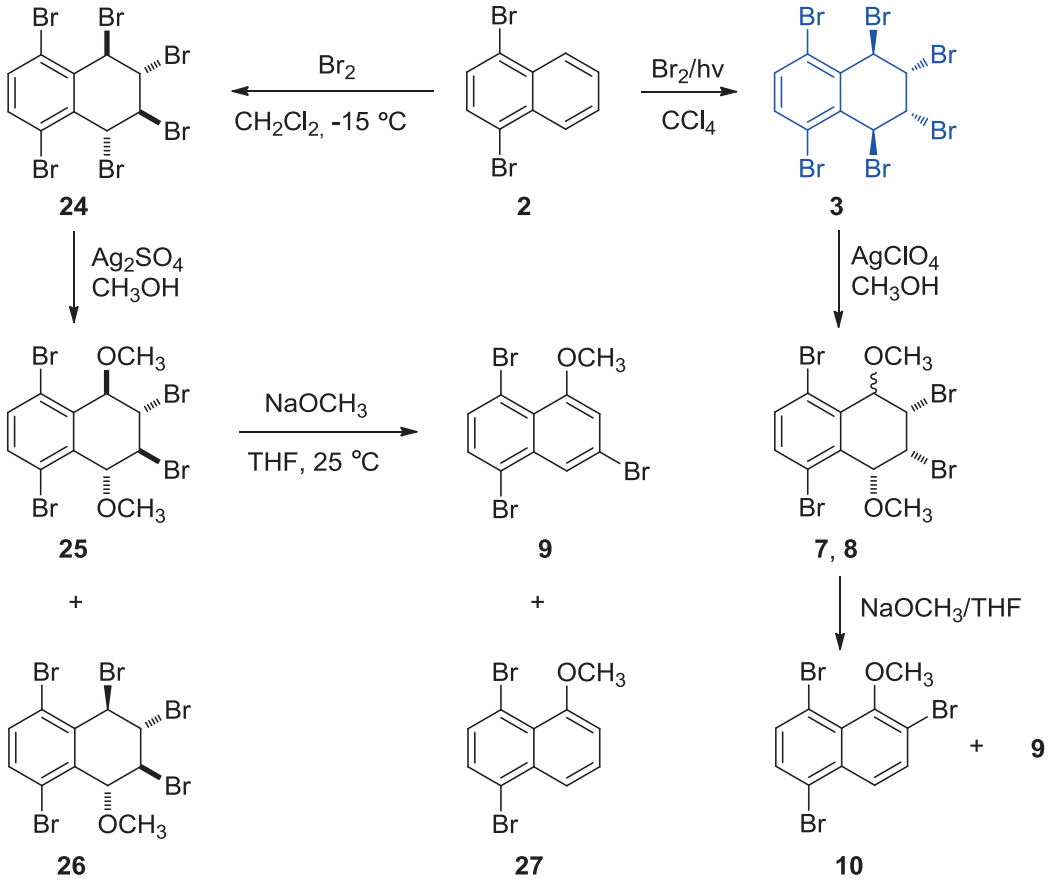


Scheme 8. Base-induced elimination and thermolysis of hexabromide **3**.

The ^{1}H NMR spectrum of tribromide **21** exhibited a singlet of H_2 and H_3, a meta coupling doublet ($J_{5,7}$= 2 Hz) for H_5, and an AB system for H_7 and H_8. In the ^{13}C NMR spectrum ten lines in the aromatic region support the suggested structure. The ^{1}H and ^{13}C NMR spectra of tetrabromide **22** indicate symmetry in its structure. Proton NMR spectra exhibited two singlets at δ 8.50 and 7.62. Five lines in the ^{13}C NMR signals are consistent with the assigned structure.

It is clear that tetrabromide is a good precursor for the corresponding methoxy derivatives of naphthalene. Therefore, tetrabromide **22** was treated with sodium methoxide in DMF in the presence of copper iodide. Copper-assisted nucleophilic substitution afforded corresponding tetramethoxide **23** as the sole product (Scheme 8). The structure of **23** was proved by its ^{1}H NMR spectrum. The mass spectral analysis of compound **23** confirmed the molecular ion at m/z 248 and ^{13}C NMR was also in agreement with the structure.

In our previous study,[8] we explored the synthesis, methanolysis reactions, and aromatization of hexabromide **24** (Scheme 9). In that reaction, aromatization of dimethoxy tetralin **25** with sodium methoxide gave tribromide **9** and dibromide **27** (Scheme 9). The same reaction for stereoisomeric dimethoxy tetralins **7** and **8** afforded tribromonaphthalenes **9** and **10**.

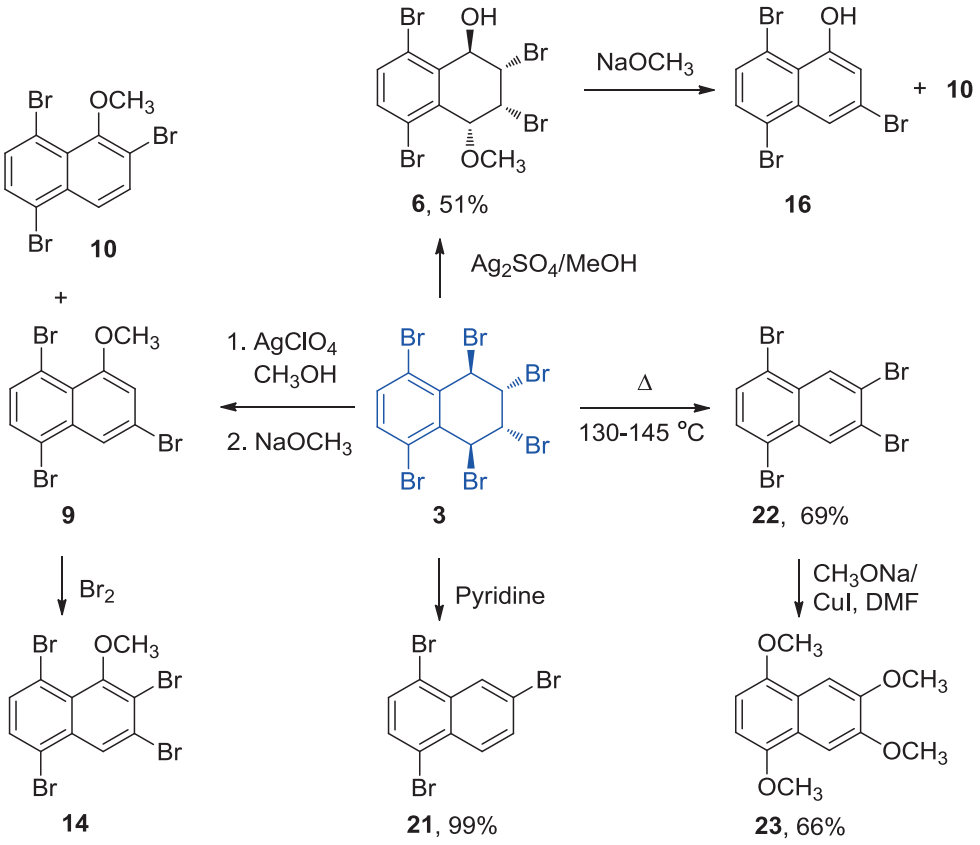


Scheme 9. Synthesis of tribromo methoxynaphthalenes from 1,4-dibromonaphthalene (**2**).

On the other hand, reaction of **3** with Ag_2SO_4 gave mainly hydroxyl compound **6**, whereas the same reaction using the reagent $AgClO_4$ produced dimethoxy compounds (**7** and **8**).

Next, the silver-promoted methanolysis of stereoisomeric hexabromide **3** followed by aromatization was discussed. The synthesis of diastereostereoisomer **7** and **8** by subsequent aromatization of **7** and **8** gave two naphthalene derivatives, **9** and **10**.

We also observed that the reactivity and selectivity of the tetralin hexabromide **3** strongly depends on both the reaction conditions and their stereochemistry as shown in the case of silver perchloride or silver sulfate (Scheme 2). Methanolysis of hexabromide **3** with silver sulfate produced an unexpected product, **6**, whose



Scheme 10. Synthesis of tetra- and penta-substituted naphthalene derivatives.

structure was established by X ray and a mechanism was suggested for the formation of hydroxyl compound **6**. We also observed that the hydroxy and methoxy compounds exhibit different reactivities towards the base. For example, while the methoxy compounds **7** and **8** (pure or mixture) give the same products (mixture of **9** and **10**), the hydroxyl compound **6** produces **10** and **16**. Further, the bromination of compound **9** and **16** was also studied. Compound **9** gives **14** while **10** did not brominate under the same reaction conditions. We also observed different reactivity of hydroxyl **16** and methoxy **9** towards bromination. It is interesting that bromination of hydroxyl **16** afforded pentabromide **18** (dibromination), whereas methoxy **9** reacted with only one equiv of bromine (monobromination) in the same reaction conditions.

These studies showed that both hexabromide **3** and 1,4-dimethoxy compounds **7** and **8** are useful intermediates for polyfunctionalization of naphthalenes. It is noteworthy that separation and crystallization of methoxylated bromonaphthalenes are relatively easy compared to bromonaphthalenes, and this offers important advantages for preparative purposes.

On the other hand, aromatization of hexabromide **3** opened up an efficient synthetic methodology for both tribromide **21** and tetrabromide **22**, which enables synthesis of the corresponding tri- and tetrasubstituted naphthalene derivatives due to the bromine groups. Treatment of hexabromide **3** with pyridine afforded tribromide **21** in high yields as the sole product, while thermolysis of hexabromide **3** mainly gave tetrabromide **22**, which is easily separated from the mixture with a simple crystallization method.

Tetrabromide **22** is good precursor for corresponding tetrasubstituted naphthalenes as shown by the synthesis of tetramethoxy naphthalene **23**.

3. Experimental

3.1. General

Thin layer chromatography was carried out on Merck silica F254 0.255 mm plates and spots were visualized with UV fluorescence at 254 nm. Classic column chromatography was performed using Merck 60 (70–230 mesh) silica gel. Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Solvents were concentrated at reduced pressure. IR spectra were recorded on a Jasco FT/IR 430 instrument. Mass spectra were recorded on GC-MS PerkinElmer Clarus 500 under electron impact (EI) conditions. ^{1}H and ^{13}C NMR spectra were recorded on a 400 (100) MHz Bruker spectrometer with $CDCl_3$ as solvent. The single crystal of the racemate **6** was used for data collection on a Bruker SMART BREEZE CCD diffractometer. Starting material 1,4-dibromonaphthalene (**2**) was prepared according to our previous method starting from naphthalene **1** or 1-bromonaphthalene.[6]

3.2. Reaction of hexabromide 3 with silver sulfate

To a solution of hexabromide **3** (obtained from bromination of 1,4-dibromonaphthalene (**2**) (0.583 g, 0.963 mmol) in dry methanol (90 mL)) was added Ag_2SO_4 (0.660 g, 2.12 mmol) under a nitrogen gas atmosphere in the dark at room temperature. The resulting reaction mixture was stirred magnetically at room temperature for 4 days. Reaction progress was monitored by TLC and ^{1}H NMR. After the removal of the silver bromide by filtration, the reaction material was diluted with dichloromethane (100 mL) and washed with H_2O (3 × 50 mL). The organic layer was dried over Na_2SO_4 and concentrated at reduced pressure. The residue (380 mg) was analyzed by ^{1}H NMR. Product ratios were 68:16:7:4:5 for **6**, **7**, **8**, **9**, and **10**, respectively. Recrystallization from dichloromethane–hexane mixture in the refrigerator gave the hydroxymethoxide **6**.

cis,cis,trans-2,3,5,8-Tetrabromo-4-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (6): Colorless crystals, yield 51%, 244 mg, mp 155–157 °C, R_f = 0.60 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (A part of AB system, $J_{6,7}$ 8.4 Hz, 1H, H_6), 7.49 (B part of AB system, $J_{6,7}$ 8.4 Hz, 1H, H_7), 5.48 (brt, 1H, H_1), 5.06 (dd, $J_{3,4}$ 4 Hz, $J_{2,3}$ 2.8 Hz, 1H, H_3), 4.72 (d, $J_{3,4}$ 4 Hz, 1H, H_4), 4.62 (brt, 1H, H_2), 3.97 (s, 3H, OCH_3), 2.86 (d, $J_{1,OH}$ 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 135.4, 135.2, 134.5, 125.6, 124.6, 78.7, 73.8, 63.7, 51.9, 48.9; MS (GCMS) m/z 494 (M^+), 415 (M^+-Br), 397 (M^+-Br-H_2O-H), 379/381/383/385 (M^+-Br-OCH_3-4H), 362/364/366/368 (M^+-Br-H_2O-OCH_3-4H), 353, 331/333/335 (M^+-2Br-3H), 314/316/318 (M^+-2Br-H_2O-2H), 300/302/304 (M^+-2Br-OCH_3-2H), 284/286/288 (M^+-2Br-H_2O-OCH_3-2H), 271/273/275, 252/254 (M^+-3Br-2H), 236/238, 222/224 (M^+-3Br-OCH_3-H), 207, 193/195, 174 (M^+-4Br), 167, 156 (M^+-4Br-H_2O), 143 (M^+-4B-OCH_3), 126, 115, 113, 102, 98, 87, 74, 63, 57, 50, 45, 39; IR (ν_{max}, cm^{-1}): 3455, 3060, 2971, 2933, 2840, 1733, 1716, 1698, 1683, 1652, 1635, 1616, 1558, 1540, 1521, 1508, 1438, 1411, 1390, 1363, 1338, 1315, 1253, 1224, 1193, 1135, 1122, 1060, 1018, 952, 923, 842, 809, 771, 754, 642, 605, 578, 526, 418; Anal. Calcd for $C_{11}H_{10}Br_4O_2$ (493.81): C, 26.75; H, 2.04%. Found: C, 26.78; H, 2.04%.

Preparative thin-layer chromatography of the residue on silica gel with ethyl acetate–hexane (1:9) gave four products.

The first fraction: **3,5,8-Tribromo-1-methoxynaphthalene (9).** Colorless crystals, yield 2%, 7 mg, mp 125–127 °C, R_f = 0.78 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, $J_{2,4}$ 2 Hz, 1H, H_4), 7.63 (A part of AB system, $J_{6,7}$ 8 Hz, 1H, H_5), 7.58 (B part of AB system, $J_{6,7}$ 8 Hz, 1H, H_8), 7.07 (d, $J_{2,4}$ 2 Hz, 1H, H_3), 3.99 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 135.5, 133.1, 131.5, 123.5,

122.7, 122.2, 121.2, 116.7, 111.3, 55.9 (OCH_3); MS (GCMS) m/z 392/394396/398 (M^+-2H), 377/379/381/383 (M^+-CH_3-2H), 362/364/366/368 (M^+-OCH_3), 349/351/353/355, 315 (M^+-Br), 300, 284 (M^+-OCH_3-Br), 270/272/274, 234/236 (M^+-2Br), 221, 204, 206 (M^+-OCH_3-2Br), 191/193, 167, 155 (M^+-3Br), 141, 125 (M^+-OCH_3-3Br), 117, 112, 102, 98, 96, 86, 74, 62, 56, 50, 38; IR (ν_{max}, cm^{-1}): 3087, 3002, 2956, 2923, 2852, 1843, 1714, 1697, 1683, 1635, 1596, 1575, 1556, 1488, 1457, 1442, 1382, 1349, 1290, 1255, 1195, 1178, 1126, 1087, 995, 906, 836, 821, 808, 765, 665, 580; Anal. Calcd for $C_{11}H_7Br_3O$ (394.88): C, 33.46; H, 1.79%. Found: C, 33.52; H, 1.78%.

The second fraction: **2,5,8-Tribromo-1-methoxynaphthalene (10)**. Colorless crystals, yield 1%, 3 mg, mp 111–112 °C, R_f = 0.85 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (A part of AB system, $J_{6,7}$ 9.2 Hz, 1H, H_7), 7.77 (B part of AB system, $J_{6,7}$ 9.2 Hz, 1H, H_6), 7.70 (A part of AB system, $J_{3,4}$ 8 Hz, 1H, H_4), 7.61 (B part of AB system, $J_{3,4}$ 8 Hz, 1H, H_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$)δ 153.0, 134.3, 134.0, 132.3, 130.8, 128.2, 125.5, 123.0, 117.6, 115.4, 62.4; MS (GCMS) m/z 392/394/396/398 (M^+-2H), 377/379/381/383 (M^+-CH_3-2H), 349/351/353/355, 316 (M^+-Br), 301, 284 (M^+-OCH_3-Br), 270/272/274, 252, 236 (M^+-2Br), 219, 206 (M^+-OCH_3-2Br), 204, 191/193, 165, 155 (M^+-3Br), 141/143, 136, 125 (M^+-OCH_3-3Br), 119, 112, 98, 86, 77, 74, 69, 62, 55, 50, 38; IR (ν_{max}, cm^{-1}): 3068, 2998, 2931, 2846, 1866, 1749, 1716, 1698, 1683, 1652, 1575, 1548, 1452, 1392, 1319, 1280, 1232, 1180, 1068, 981, 906, 819, 802, 786, 769, 678, 628; Anal. Calcd for $C_{11}H_7Br_3O$ (394.88): C, 33.46; H, 1.79%. Found: C, 33.55; H, 1.78%.

The third fraction: **cis,cis,trans-2,3,5,8-tetrabromo-1,4-dimethoxy-1,2,3,4-tetrahydronaphthalene (7).** Colorless crystals, yield 7%, 32 mg, mp 155–157 °C, R_f =0.60 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.52 (m, 2H, H_6 and H_7), 5.00 (m, 1H, H_4), 4.96 (m, 1H, H_1), 4.74 (m, 2H, H_2 and H_3), 4.00 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 135.1, 134.6, 133.6, 126.2, 125.4, 82.5, 78.8, 64.5, 58.9, 48.4; MS (GCMS) m/z 425/427/429/431 (M^+-Br-H), 393/395/397/399 (M^+-Br-OCH_3-4H), 362/364/366/368 (M^+-Br-2OCH_3-2H), 353, 347 (M^+-2Br-H), 333, 314/316/318 (M^+-2Br-OCH_3-3H), 301, 289, 286 (M^+-2Br-2OCH_3), 271/273/275, 263, 251, 236/238, 223, 206, 193/195, 169, 158, 143, 126, 113, 102, 99, 87, 75, 63, 50, 45, 39; IR (ν_{max}, cm^{-1}): 3066, 2962, 2940, 2927, 2898, 2829, 1612, 1434, 1365, 1317, 1265, 1193, 1128, 1068, 973, 931, 821, 763, 692, 638, 611, 582, 534, 501, 420; Anal. Calcd for $C_{12}H_{12}Br_4O_2$ (507.84): C, 28.38; H, 2.38%. Found: C, 28.29; H, 2.38%.

The last fraction: **cis,cis,cis-2,3,5,8-tetrabromo-1,4-dimethoxy-1,2,3,4-tetrahydronaphthalene (8).** Colorless crystals, yield 3%, 12 mg, mp 145–146 °C, R_f =0.42 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.49 (s, 2H, H_6 and H_7), 4.76 (A part of AA′BB′ system, 2H, H_1 and H_4), 4.63 (B part of AA′BB′, 2H, H_2 and H_3), 3.77 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$)δ 135.9, 135.0, 124.8, 78.7, 60.2, 50.8; MS (GCMS) m/z 446 (M^+-2OCH_3), 425/427/429/431 (M^+-Br-H), 397 (M^+-Br-OCH_3), 363/365/367/369 (M^+-Br-2OCH_3-3H), 346 (M^+-2Br-2H), 331, 316 (M^+-2Br-OCH_3-H), 307, 303, 284/286/288 (M^+-2Br-2OCH_3), 271/273/275, 263, 251, 236/238, 223, 207, 193/195, 182, 169, 158, 143, 126, 113, 99, 87, 75, 63, 56, 50, 45, 39; IR (ν_{max}, cm^{-1}): 3056, 2956, 2927, 2913, 2821, 1731, 1558, 1538, 1457, 1430, 1396, 1340, 1322, 1301, 1265, 1226, 1191, 1135, 1076, 1020, 968, 910, 809, 765, 744, 624, 543, 528, 474, 433, 410; Anal. Calcd for $C_{12}H_{12}Br_4O_2$ (507.84): C, 28.38; H, 2.38%. Found: C, 28.45; H, 2.37%.

3.3. Reaction of hexabromide 3 with 2 equiv silver perchlorate

To a stirred solution of hexabromide **3** (0.950 g, 1.57 mmol) in dry and freshly distilled methanol (140 mL) was added silver perchloride (0.715 g, 3.45 mmol) under an argon gas atmosphere in the dark. The resulting reaction mixture was stirred magnetically at room temperature for 6 days. Reaction progress was monitored by TLC for the consumption of the starting material. After completion of the reaction, the precipitated silver bromide was removed by filtration. The reaction mixture was diluted with methylene chloride (50 mL), washed with water (3 × 50 mL), dried over Na_2SO_4, and concentrated at reduced pressure. Then the relative percentages of the products were determined by ^{1}H NMR as 74:26 for dimethoxide **7** and dimethoxide **8**, respectively. The residue (727 mg) was chromatographed on silica gel (70 g), eluting with hexane and ethyl acetate–hexane (5:95) to give *cis,cis,trans*-2,3,5,8-tetrabromo-1,4-dimethoxy-1,2,3,4-tetrahydronaphthalene (**7**) (524 mg, 66%) and *cis,cis,cis*-2,3,5,8-tetrabromo-1,4-dimethoxy-1,2,3,4-tetrahydronaphthalene (**8**) (167 mg, 21%).

3.4. Aromatization of dimethoxides 7 and 8

To a solution of the dimethoxides **7** and **8** (^{1}H NMR rate: 67:33) (0.415 g, 0.817 mmol) in freshly distilled THF (20 mL) was added dropwise a solution of sodium methoxide (0.132 g, 2.45 mmol) in dried THF (20 mL) under argon atmosphere. The resulting reaction mixture was magnetically stirred for 12 h at 25 °C. After the reaction was complete (TLC), the reaction material was diluted with diethyl ether (50 mL) and washed with water (3 × 40 mL). After drying with sodium sulfate and removing the solvent, ^{1}H NMR of the residue (0.273 g, total yield: 85%) showed two products in a ratio of 40:60 for **9** and **10**, respectively. The residue (0.273 g) was chromatographed over silica gel (50 g). Eluting with hexane gave 1-methoxy-3,5,8-tribromonaphtlanene (**9**) (130 mg, 40%) and 1-methoxy-2,5,8-tribromonaphthalene (**10**) (87 mg, 27%).

3.5. Aromatization of hydroxymethoxide 6

A stirred solution of the hydroxymethoxide **6** (0170 g, 0.344 mmol) in dry and freshly distilled THF (20 mL) was combined with a solution of sodium methoxide (0.056 g, 1.03 mmol) in freshly distilled THF (20 mL) under argon atmosphere. The resulting reaction mixture was magnetically stirred for 12 h at 25 °C. Ether (50 mL) was added to the reaction mixture and the resulting precipitate was washed with water (3 × 40 mL) and dried over anhydride sodium sulfate. The solvent was evaporated. ^{1}H NMR of the residue (0.102 g) showed two products in a ratio of 67:33 for **10** and **16**, respectively. The residue (0.102 g) was chromatographed on silica gel (15 g), eluting with hexane to give 1-methoxy-2,5,8-tribromonaphthalene (**10**) (62 mg, 46%) and 1-hydroxy-3,5,8-tribromonaphthalene (**16**).

1-Hydroxy-3,5,8-tribromonaphthalene (16). Colorless crystals, yield 13%, 17 mg, mp 106.5–107.5 °C, R_f =0.44 (1:9 ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H, OH), 8.10 (d, $J_{2,4}$ 2 Hz, 1H, H_4), 7.61 (A part of AB system, $J_{6,7}$ 8 Hz, 1H, H_7), 7.49 (B part of AB system, $J_{6,7}$ 8 Hz, 1H, H_6), 7.29 (d, $J_{2,4}$ 1.6 Hz, 1H, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 135.6, 131.6, 131.2, 123.1, 122.9, 122.8, 120.3, 117.8, 114.9; MS (GCMS) m/z 378/380/382/384 (M^+), 351, 314, 299/301/303, 271/273/275, 235, 220/222, 193, 191, 167, 150, 143, 136, 117, 113, 96, 86, 77, 74, 63, 56, 50, 38; IR (ν_{max}, cm^{-1}): 3401, 3079, 2962, 2927, 2873, 1600, 1575, 1554, 1481, 1396, 1357, 1294, 1265, 1226, 1168, 1110, 1037, 923, 844, 831, 815, 759, 638, 582, 539; Anal. Calcd for $C_{10}H_5Br_3O$ (380.86): C, 31.54; H, 1.32%. Found: C, 31.61; H, 1.31%.

3.6. Bromination of 1-methoxy-3,5,8-tribromonaphthalene (9) with 1.2 equiv molecular bromine

The solution of 1-methoxy-3,5,8-tribromonaphthalene **9** (150 mg, 0.39 mmol) in CH_2Cl_2 (1.5 mL) was protected from light and to the solution was added Br_2 (24 mg, 0.15 mmol) in one portion. The mixture was allowed to stand at room temperature. Reaction progress was monitored by TLC. After completing the reaction in 2 days, the solvent was removed in vacuo to afford pure 2,3,5,8-tetrabromo-1-methoxynaphthalene (**14**).

2,3,5,8-Tetrabromo-1-methoxynaphthalene (14). Colorless crystals, yield 95%, 170 mg, mp 144–146 °C, R_f = 0.33 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H, H_4), 7.72 (A part of AB system, $J_{6,7}$ 8 Hz, 1H, H_6), 7.63 (B part of AB system, $J_{6,7}$ 8 Hz, 1H, H_7), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 134.5, 134.1, 131.6, 128.5, 126.8, 125.4, 121.8, 121.2, 115.6, 62.5; MS (GCMS) m/z 472/474/476 (M^+-H), 457/459/461 (M^+-H-CH_3), 429/431/433, 393, 380 (M^+-CH_3-Br), 364, 348/350/352/354, 312/314/316, 282/284/286, 269/271/273, 235, 218, 205, 190, 182, 166, 154, 142, 135, 124, 111, 102, 98, 95, 85, 74, 69, 61, 55, 50, 37; IR (ν_{max}, cm^{-1}): 3073, 2940, 2850, 1862, 1683, 1587, 1563, 1535, 1465, 1436, 1371, 1321, 1270, 1220, 1195, 1168, 1106, 1085, 981, 912, 856, 835, 817, 690, 671, 549; Anal. Calcd for $C_{11}H_6Br_4O$ (473.78): C, 27.89; H, 1.28%. Found: C, 27.91; H, 1.28%.

3.7. Bromination of 3,5,8-tribromonaphthalen-1-ol (16)

The solution of 3,5,8-tribromonaphthalen-1-ol (**16**) (50 mg, 0.026 mmol) in CH_2Cl_2 (2.5 mL) was protected from light and to the solution was added Br_2 (19 mg, 0.12 mmol) in one portion. The mixture was allowed to stand at room temperature. After completing the reaction (TLC) in 8 h the crude product was passed through a short silica gel column eluting with CH_2Cl_2 to give 2,3,4,5,8-pentabromonaphthalen-1-ol (**18**).

2,3,4,5,8-Pentabromonaphthalen-1-ol (18). Yellow crystals, yield 99%, 14 mg, mp 148–150 °C, R_f =0.46 (1:9 ethy acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (A part of AB system, $J_{6,7}$ 8.4 Hz, 1H, H_7), 7.66 (B part of AB system, $J_{6,7}$ 8 Hz, 1H, H_6), 6.13 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.7, 141.0, 137.7, 131.3, 129.2, 123.4, 123.1, 96.1; IR (ν_{max}, cm^{-1}): 3446, 3104, 3060, 2962, 2921, 2850, 1670, 1592, 1558, 1438, 1278, 1238, 1193, 1108, 1072, 916, 844, 833, 815, 707, 696, 655, 590, 522, 503, 418; Anal. Calcd for $C_{10}H_3Br_5O$ (538.65): C, 22.30; H, 0.56%. Found: C, 22.27; H, 0.56%.

3.8. Synthesis of 1,4,6-tribromonaphthalene (21)

To a solution of the hexabromide **3** (0.410 g, 0.677 mmol) in toluene (20 mL) was added freshly distilled pyridine (1.96 g, 24.8 mmol, 2 mL). The mixture was stirred magnetically at room temperature for 4 days. The mixture was filtered and pyridine and solvent were then removed in vacuo. Tribromonaphthalene **21** was purified in 99% yield (246 mg) by passing a short silica gel column eluting with hexane.

1,4,6-Tribromnaphthalene (21). Colorless crystals, yield 99%, 246 mg, mp 84–85 °C, R_f =0, 89 (hexane) (Lit.[7]: 86–87 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, $J_{5,7}$ 2 Hz, 1H, H_5), 8.13 (A part of AB system, $J_{7,8}$ 8.8 Hz, 1H, H_8), 7.72 (d of B part of AB system, $J_{7,8}$ 8.8 Hz, J_{57} 2 Hz, 1H, H_7), 7.66 (s, 2H, H_2 and H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 131.6, 131.5, 131.1, 130.5, 130.0, 129.6, 123.0, 122.5, 121.2; MS (GCMS) m/z 362/364/366/368 (M^+), 283/285/287 (M^+-Br), 204/206 (M^+-2Br), 182, 142, 125 (M^+-3Br), 103, 99, 86, 74, 62, 50; IR (ν_{max}, cm^{-1}): 3081, 3066, 2923, 2852, 1918, 1857, 1741, 1637, 1604, 1573, 1481, 1423, 1405, 1330, 1290, 1245, 1176, 1143, 1072, 964, 871, 815, 619, 484, 406; Anal. Calcd for $C_{10}H_5Br_3$ (364.86): C, 32.92; H, 1.38%. Found: C, 32.97; H, 1.39%.

3.9. Synthesis of 1,4,6,7-tetrabromonaphthalene (22)

Hexabromide **3** (1.295 g, 2.13 mmol) was put into a round bottom flask and heated by a heating mantle at 130–145 °C for 10 h. ^{1}H NMR investigation of the reaction mixture (871 mg) showed formation of tetrabromide **22**, tribromide **21**, and 1,4-dibromide **2** in a ratio of 79:16:5, respectively. The solid was purified by repeated crystallization procedures from dichloromethane to give pure tetrabromide **22**.

1,4,6,7-Tetrabromonaphthalene (22). Colorless crystals, yield 69%, 652 mg, mp 169–170 °C (lit.[7]: 168–169 °C), R_f =0.87 (hexane). ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.50 (s, 2H, H_5 and H_8), 7.62 (s, 2H, H_2 and H_3); ^{13}C NMR (100 MHz, $CDCl_3$)δ 132.4, 132.3, 131.3, 125.5, 121.0; MS (GCMS) m/z 440/442/444/446/448 (M^+), 361/363/365/367 (M^+-Br), 282/284/286 (M^+-2Br), 222, 203/205 (M^+-3Br), 181, 154, 142, 124, 190 (M^+-4CH_3), 175, 160, 147, 131, 124 (M^+-4Br), 101, 98, 85, 74, 62, 50, 37; IR (ν_{max}, cm^{-1}): 3073, 1863, 1739, 1643, 1562, 1457, 1403, 1294, 1247, 1191, 1170, 1110, 970, 875, 831, 819, 617; Anal. Calcd for $C_{10}H_4Br_4$ (443.75): C, 27.07; H, 0.91%. Found: C, 27.08; H, 0.90%.

3.10. Synthesis of 1,4,6,7-tetramethoxynaphthalene 23

Freshly cut sodium (0.415 g, 18 mmol) was added to dry methanol (20 mL) under argon atmosphere. When dissolution was completed, the warm solution was diluted with dry DMF (10 mL), which was followed by the addition of copper(I) iodide (0.429 g, 2.25 mmol). After dissolution, 1,4,6,7-tetrabromonaphthalene (**22**) (0.5 g, 1.13 mmol) in dry DMF (30 mL) was added. The reaction mixture was stirred magnetically under argon gas atmosphere at reflux for 5 days. Reaction progress was monitored by TLC. After cooling to room temperature, diethyl ether (70 mL) was added to the reaction, followed by washing with H_2O (4 × 50 mL). Then the organic layer was separated, dried over Na_2SO_4, and concentrated at reduced pressure. 1,4,6,7-Tetramethoxynaphthalene (**23**) was obtained in 66% yield (184 mg) after recrystallization of the crude product.

1,4,6,7-Tetramethoxynaphthalene (23). Colorless crystals, yield 66%, 184 mg, mp 117–119 °C, R_f =0.39 (1:9 ethylacetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2H, H_5 and H_8), 6.64 (s, 2H, H_2 and H_3), 4.05 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 148.6, 121.5, 101.9, 101.1, 55.9, 55.6; MS (GCMS) m/z 248 (M^+), 233 (M^+-CH_3), 218 (M^+-2CH_3), 203 (M^+-3CH_3), 190 (M^+-4CH_3), 175, 160, 147, 131, 124, 119, 101, 91, 89, 76, 63, 50, 39; IR (ν_{max}, cm^{-1}): 3091, 2999, 2956, 2931, 2829, 2055, 1949, 1749, 1708, 1679, 1602, 1511, 1484, 1461, 1452, 1427, 1334, 1265, 1205, 1176, 1089, 1014, 970, 862, 811, 784, 723, 568; Anal. Calcd for $C_{14}H_{16}O_4$ (248.27): C, 67.65; H, 6.50%. Found: C, 22.27; H, 6.53%.

3.11. X-ray analysis

The single crystal of the racemate **6** was used for data collection on a Bruker SMART BREEZE CCD diffractometer. The graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) and oscillation scans technique with $\Delta\omega = 5^\circ$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma$ (F^2). Integration of the intensities, correction for Lorentz and polarization effects, and cell refinement was performed using Bruker SAINT (Bruker AXS Inc., 2012) software.[9] The structure was solved by direct methods using *SHELXS-97*[10] and refined by a full-matrix least-squares procedure also using *SHELXL-97*.[9] H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* **9**: $C_{15}H_{12}Br_4O_2$; crystal system, space group: orthorhombic, $P2_12_12_1$; (no: 19); unit cell dimensions:

a = 10.9427(5), b = 22.4790(11), c = 20.1385(9) Å, α = 90, β = 90, γ =90°; volume: 4953.7(4) Å^3; Z = 12; calculated density: 2.188 g cm^{-3}; absorption coefficient: 9.749 mm^{-1}; F(000): 3096; θ-range for data collection 1.4–28.5°; refinement method: full-matrix least-square on F^2; data/parameters: 6837/569; goodness-of-fit on F^2: 0.920; final R indices [$I > 2\sigma(I)$]: R_1 = 0.056, wR_2 = 0.111 largest diff. peak and hole: 0.831 and –0.782 e Å^{-3}.

The crystallographic data (excluding structure factors) were deposited in CCDC-1038474 registration number and are available free of charge upon request to CCDC, 12 Union Road, Cambridge, UK (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk).

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