Tetrahedron 67 (2011) 3483–3489

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Selective O-demethylation during bromination of (3,4-dimethoxyphenyl)(2,3,4-trimethoxyphenyl)methanone

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ARTICLE INFO

Article history:
Received 4 December 2010
Received in revised form 23 February 2011
Accepted 14 March 2011
Available online 21 March 2011

Keywords:
Bromophenol
Bromination
Selective O-demethylation

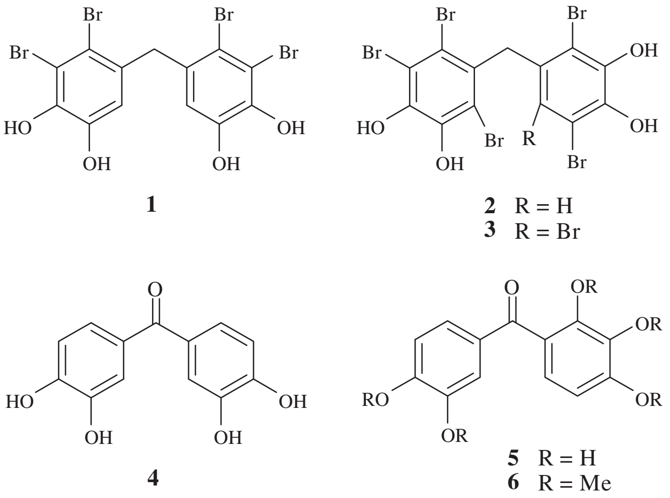
ABSTRACT

(3,4-Dimethoxyphenyl)(2,3,4-trimethoxyphenyl)methanone was synthesized and its bromination was investigated in different conditions. Nine new products (bromophenol derivatives) were isolated in the reactions. These bromophenol derivatives were obtained by selective O-demethylation in its bromination with bromine. The products and their formations were discussed.

1. Introduction

Organohalogens, especially organobromides, serve as starting materials for many target molecules. Organobromides,[1] such as bromophenols are important compounds. For example, bromophenol **1** exhibits enzyme inhibition,[2] cytotoxicity,[3] feeding deterrent,[4] and microbial[5] activities. Antioxidant activities[6] of bromophenols **1**, **3**, and **4** and significant aldose reductase inhibitory activity[7] of bromophenols **2** and **3** were also noted (Scheme 1).

Brominated derivatives of compound **4** also have important antioxidant activities.[6a] Compound **5**, in similar to **4**, and its brominated derivatives are potential biologically active compounds. For the synthesis of compound **5** and its derivatives with Br, compound **6** should be synthesized and then its bromination and demthylation reactions should be realized because phenolic OH groups are usually protected as arylmethylethers in synthesis.[6a,8] Furthermore, interesting products including Br, OH, and OMe groups may be observed. Therefore, the synthesis of compound **6** and its brominations were investigated.



Scheme 1.

2. Result and discussion

(3,4-Dimethoxyphenyl)(2,3,4-trimethoxyphenyl)methanone (**6**) was obtained from the reaction of 3,4-dimethoxybenzoic acid (**7**) and 1,2,3-trimethoxybenzene (**8**) in polyphosphoric acid (PPA) by the literature method (Scheme 2).[6a,8c,d]

Brominations of compound **6** under different conditions were investigated for the synthesis of its new brominated derivatives. Selectively, aromatic compounds with ceric ammonium nitrate (CAN)/LiBr react to give brominated product(s).[9] Bromination of **6** with 1.1 and 2.2 equiv of LiBr/CAN at rt gave a monobromide and a mixture of mono- and dibromides, respectively (Scheme 3, Table 1).

An AB-system in the ^{1}H NMR spectrum of monobromide is similar to that of aromatic ring with two OMe of **6**. Electrophilic

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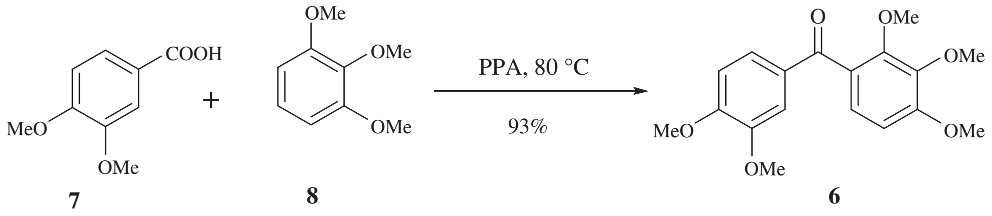
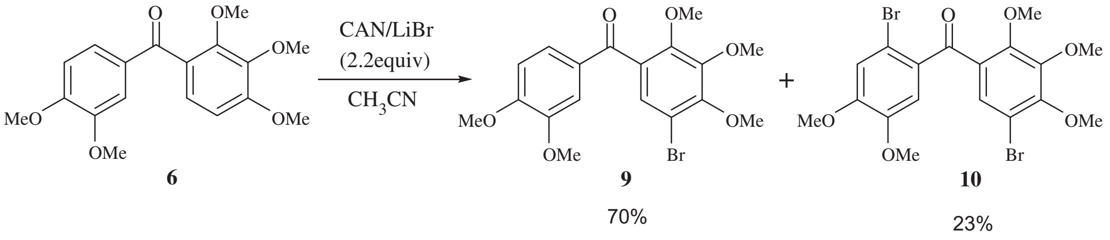
doi:10.1016/j.tet.2011.03.033



Scheme 2.



Scheme 3.

Table 1
Bromination reactions of the compound **6** (1.0 equiv) at different conditions and yields % of the product(s)

R (E)	*T* (Time)	% Yields of the product (s)								
		9	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**18**
LiBr (1.1)/CAN (1.1)[a]	rt (1 d)	97	—	—	—	—	—	—	—	—
LiBr (2.2)/CAN (2.2)[a,d]	rt (15 d)	—	25	75	—	—	—	—	—	—
LiBr (6.0)/CAN (6.0)[a]	rt (6 d)	—	95	—	—	—	—	—	—	—
Br_2 (1.1)[b]	rt (1 d)	96	—	—	—	—	—	—	—	
Br_2 (2.2)[b,d]	rt (2.5 d)	—	88	12	—	—	—	—	—	—
Br_2 (10.0)[b]	rt (8 d)	—	2	1.4	73	13	2.4	—	—	
Br_2 (6.0)[b]	Ref. (3 d)	—	20	1.9	68	6	1.6	—	—	—
Br_2 (10.0)[b]	Ref. (8 d)	—	3	1.5	74	11	2.1	—	—	—
Fe (powder)/Br_2 (10.0)[c]	Ref. (5 h)	—	—	—	—	—	—	5	19	63
Fe (powder)/Br_2 (10.0)[d]	Ref. (1.5 h)	—	—	—	—	—	—	8	33	59

(R=Reagent(s), E=equivalent, CAN=Ceric ammonium nitrate, T=Temperature, rt=Room temperature, d=Day, h=Hour, Ref.=Reflux).

[a] (CH_3CN)

[b] ($CHCl_3$)

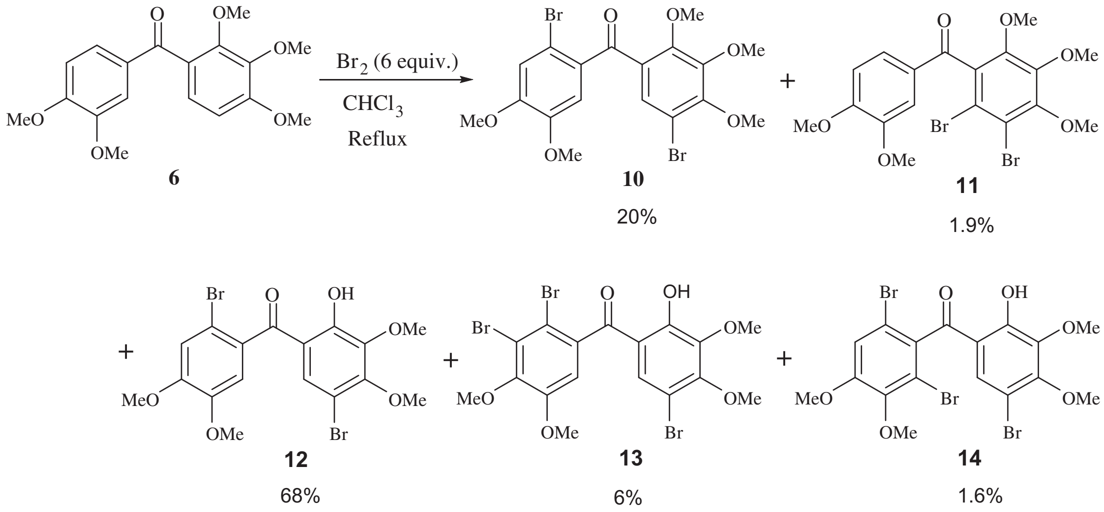
[c] (HOAc) are the solvent of the reactions.

[d] Percent of products in the mixture (according to ^{1}H NMR)

substitution of bromine should be in the *meta* position with respect to CO group in the ring with three OMe of **6** because of the electron density of this ring and the orientations of CO and OMe groups. Monobromide should be structure **9**. Chromatography on silica gel of the mixture obtained from bromination of **6** with 2.2 equiv of LiBr/CAN permitted the isolation of monobromide **9** and a dibromide. The structure of dibromide should be **10** because three peaks were present as singlet(s) while no AB-system was present in the aromatic region of its ^{1}H NMR spectrum. Dibromide **10** should be formed of a reaction of bromine with monobromide **9**.

Bromination of **6** with 6.0 equiv of LiBr/CAN at rt gave dibromide **10** as the sole product (Table 1). Bromination of **6** with 1.1 and 2.2 equiv of Br_2 at rt gave monobromide and a mixture of mono- and dibromides, respectively (Table 1).

A solution in $CHCl_3$ of **6** with Br_2 (6.0 equiv) at reflux temperature was reacted to give five products (Scheme 4, Table 1). According to NMR, they are two dibromides and three bromophenols. One of the dibromides is **10** and the other dibromide has an AB-system whose peaks at 7.20 ppm as dd (J=1.9, 8.4 Hz) and at 6.84 ppm as d (J=8.4 Hz) are similar to those of the aromatic ring with two OMe of **6**. Therefore, this dibromide should be structure **11**.



Scheme 4.

It was seen that OCH_3 groups were demethylated into OH groups in the reaction condition because the ^1H NMR spectra of bromophenols include one (OH) peak at 12.27–12.06 ppm and four (OCH_3) peaks at 4.09–3.87 ppm as s. One of the bromophenols has three signals (at 7.26, 7.11 and 6.81 ppm) with a 1:1:1 ratio for the aromatic hydrogens. This bromophenol should be a dibromophenol. Each of the other two bromophenols has two signals (at 7.17–6.80 ppm) whose ratio is 1:1 for aromatic hydrogens. Therefore, each of these bromophenols should be three bromophenols.

It may mentioned that there is a hydrogen bond between the OH and CO groups in the bromophenols because they resonate at lower fields (at 12.27–12.06 ppm for OH and 199.5–197.6 ppm for CO) than the others, such as **6**, **9** and **10** (at 193.0–192.9 ppm for CO). According to the NMR spectra, the structures of dibromo- and tribromo-phenols may be **12**–**14**, respectively. To make sure that the positions of the aromatic hydrogen atoms of bromophenols stated **12**–**14**, their exact structures were determined by X-ray diffraction analysis (Fig. 1). In the structures carbon-bromine distance varies in the range of 1.886(3)–1.900(4) Å. Phenolic rings significantly twisted with respect to each other depending on the substituted moeities and their positions. Dihedral angles formed by LSQ-planes are as follows; 85.8(2)°, 75.8(2)° and 84.9(2)° for compounds **12**–**14**, respectively. Also there are intramolecular hydrogen bonds in all three structures.

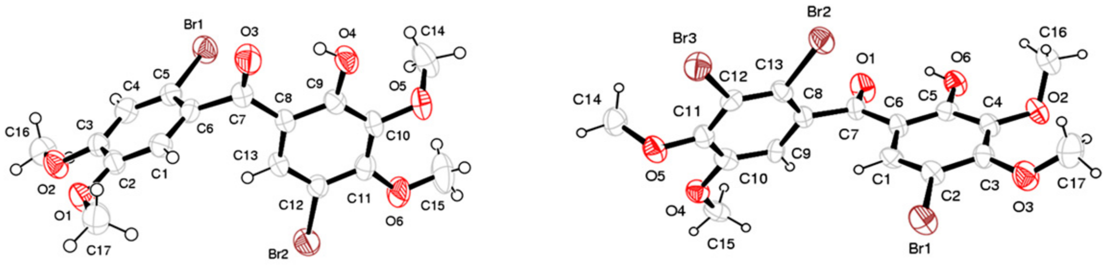
Another method for bromination with Fe/Br_2 in acetic acid (HOAc) was examined. Ketone **6** was heated to reflux with Fe/Br_2 in HOAc at 130±5 °C for 5 h and three products were isolated in this bromination reaction by column chromatography (Scheme 5, Table 1). Based on the NMR spectra of these compounds, it was determined that they are tribromide, tetrabromide, and tribromodimethoxybenzene. It was not easy to establish the positions of the aromatic hydrogen atoms in tribromide and tetrabromide. Therefore, their exact structures were determined by X-ray diffraction analysis as **15** for tribromide and **16** for tetrabromide (Fig. 2). The conformation and location of bromine and the methoxy groups is shown in Fig. 2.

The tribromodimethoxybenzene formed by bond cleavage could be one of two isomers whose structures are known to be 1,2,3-tribromo-4,5-dimethoxybenzene (**18**) and 1,2,5-tribromo-3,4-dimethoxybenzene because OMe groups are in vicinal position.[8c,10] The NMR data of 1,2,5-tribromo-3,4-dimethoxybenzene has been reported in literature[8c] while that of **18** is absent.[10a] The NMR data of the formed tribromodimethoxybenzene is not consistent with 1,2,5-tribromo-3,4-dimethoxybenzene, but its melting point (82–84 °C, 86 °C[10a]) is consistent with **18**. The formation of **18** should have formed as a result of the reaction of tetrabromide **16** with Br^+ via **17**.

Bromination reactions of compound **6** under different conditions were given Table 1. The products and their ratios depend on the reaction conditions. With LiBr/CAN at rt, compounds **9** and **10** were obtained as sole products while products further bromine were not obtained. Brominated all products were obtained with molecular Br_2 under different conditions. Bromophenols **12**–**14** should be formed from the corresponding bromides **19**. Bromophenols **12**–**14** were formed during brominations of ketone **6** by selective O-demethylation.

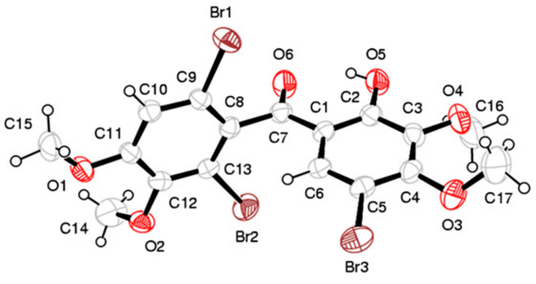
To our knowledge, selective O-demethylation during bromination is unknown. As mentioned above, there are five OMe groups in the compounds such as **10**. Two OMe groups of them are one ring while the others are also other ring. Only, *ortho* (according to CO) OMe groups were converted into OH groups from these OMe groups. There is a similar selective O-demethylation with reagents such as HCl, HBr, $BeCl_2$ in the literature.[11]

For selective O-demethylation during the bromination of **6**, the oxygen atom *ortho* to the CO group and carbon atom of CH_3, which is bound to this oxygen should be less electron-rich. Two reasons may be mentioned for this. The first is inductive effect of CO group while the other is the hydrogen bond between oxygen of CO and *ortho* OMe like **22** and **23** (Scheme 5). The hydrogen bond is favored to the inductive effect of CO group. HBr formed of the electrophilic substitution of bromine with bromides **19**, which convert into **12**–**14**, was reacted to give intermediate **20**. Compound **20** is then converted into **23** via **22** and then methyl group of *ortho* OMe in **23** reacts with Br^- to give MeBr and bromophenols **12**–**14** by S_N2 (Scheme 6).



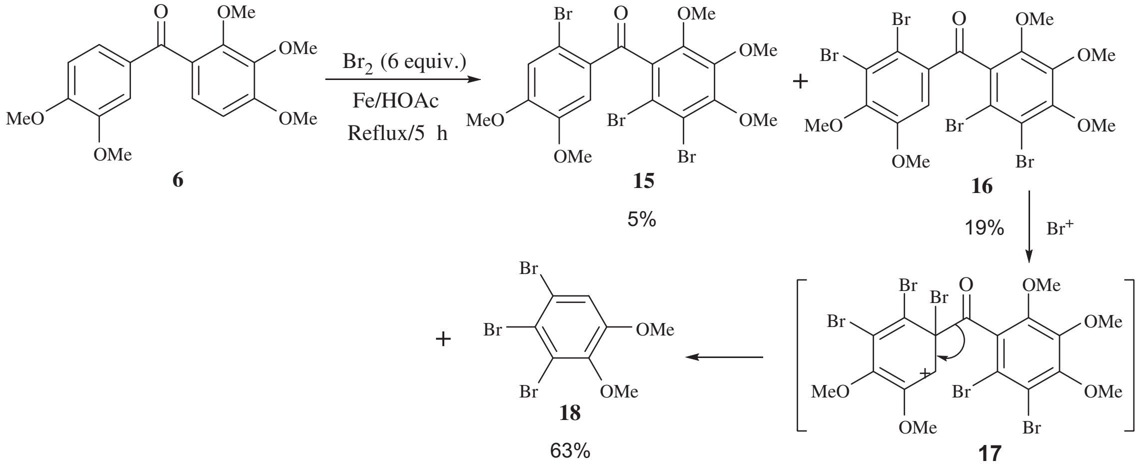
Dibromophenol **12**

Tribromophenol **13**

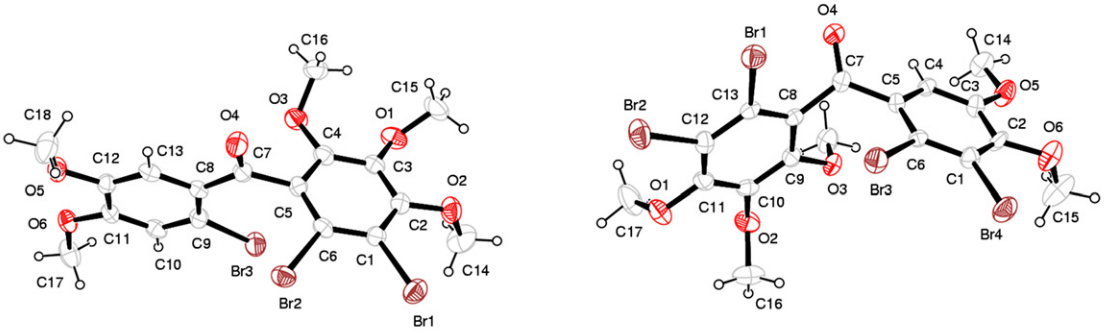


Tribromophenol **14**

Fig. 1. The molecular structures of bromophenols **12**–**14**. Displacement ellipsoids are shown at the 50% probability level.

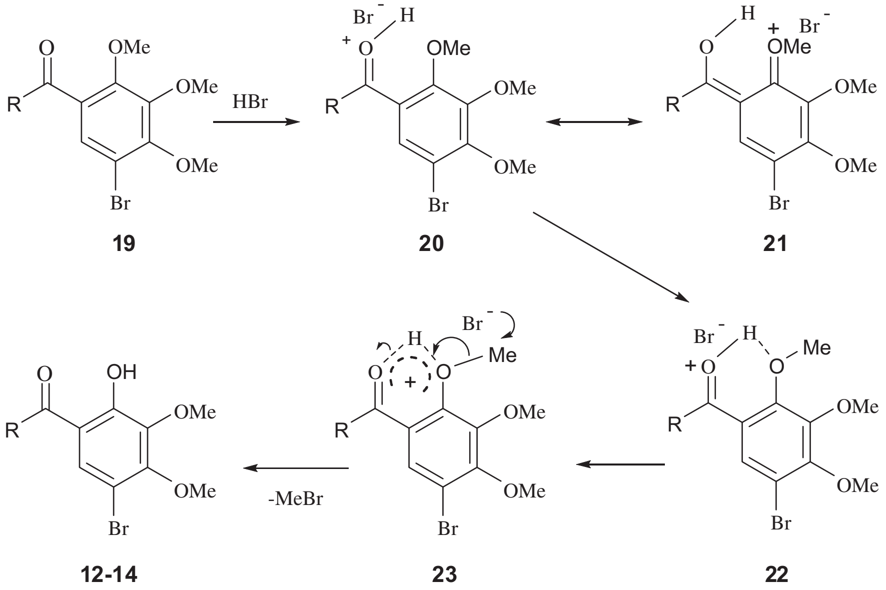


Scheme 5.



Tribromide **15** Tetrabromide **16**

Fig. 2. The molecular structures of bromides **15** and **16**. Displacement ellipsoids are shown at the 50% probability level.



Scheme 6.

3. Conclusion

(3,4-Dimethoxyphenyl)(2,3,4-trimethoxyphenyl)methanone (**6**) was obtained from the reaction of acid **7** and 1,2,3-trimethoxybenzene (**8**) in PPA. Depending upon the number of equivalents of LiBr/CAN and **6** at rt, monobromide **9** and dibromide **10** were obtained as the sole products while products with more Br than the two were not obtained. The formation of brominated all products with Br **9**–**14** from ketone **6** and molecular Br_2 depend on different conditions such as the number of equivalents of Br_2 and time, temperatures and catalyst of the reaction.

Bromophenols **12**–**14** were formed during brominations of ketone **6** with Br_2. It was accepted that bromophenols **12**–**14** were formed from the reactions of corresponding bromides (**19**) with HBr by selective O-demethylation. To our knowledge, selective O-demethylation during bromination is not known. By this method, aromatic compounds, such as ketone **6** including CO groups may be converted into corresponding bromophenols.

4. Experimental

4.1. General

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Melting points were determined on a capillary melting apparatus (BUCHI 530) and are uncorrected. IR spectra were obtained from solutions in 0.1 mm cells with a Perkin–Elmer spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a 200 (50) and 400 (100)-MHz Varian spectrometer; δ in parts per million, Me_4Si as the internal standard. Elemental analyses were performed on a Leco CHNS-932 apparatus. All column chromatography was performed on silica gel (60-mesh, Merck). PLC is preparative thick-layer chromatography: 1 mm of silica gel 60 PF (Merck) on glass plates.

4.2. Synthesis of (3,4-dimethoxyphenyl)(2,3,4-dimethoxyphenyl)methanone (6)

Polyphosphoric acid (PPA), which was prepared from concd H_3PO_4 (85%, 16.0 g) and P_2O_5 (28.2 g, 0.2 mol), was heated to 80 °C in a beaker (150 mL) and mixed. To this mixture were added trimethoxybenzene (4.62 g, 27.5 mmol) and **7** (5.0 g, 27.5 mmol) quickly. The mixture was stirred with a glass stick at 80 °C for 1.5 h and then was carefully poured onto 35 mL of ice/water. The organic phase was extracted with ethyl acetate (EtOAc) (2x125 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. Ketone **6** (9.1 g, 94%) was the sole product and was crystallized from EtOAc/hexane as colorless block crystals. Mp 117–119 °C: δ_H (400 MHz, $CDCl_3$), 7.51 (br d, J=2.0 Hz, aromatic, 1H), 7.29 (dd, A part of AB-system, J=2.0, 8.4 Hz, aromatic, 1H), 7.06 (d, A part of AB-system, J=8.6 Hz, 1H), 6.83 (d, B part of AB-system, J=2.0 Hz, J=8.4 Hz, aromatic, 1H), 6.70 (d, B part of AB-system, J=8.6 Hz, aromatic, 1H), 3.92 (s, OCH_3, 3H), 3.91 (s, OCH_3, 3H), 3.90 (s, OCH_3, 3H), 3.88 (s, OCH_3, 3H), 3.76 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 194.3 (CO), 155.9 (CH), 153.5 (C), 152.5 (C), 149.1 (C), 142.3 (C), 131.3 (C), 127.0 (C), 125.8 (CH), 124.7 (CH), 111.5 (C), 110.0 (CH), 107.0 (CH), 62.1 (OCH_3), 61.2 (OCH_3), 56.3 (OCH_3), 56.3 (OCH_3), 56.2 (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 2943, 2839, 1646, 1593, 1514, 1496, 1462, 1417, 1273, 1183, 1140, 1097, 1055, 1037, 1021, 988, 920. Anal. Calcd for ($C_{18}H_{20}O_6$): C 65.05, H 6.07. Found C 64.79, H 6.06.

4.3. Standard procedure for the selective bromination of ketone 6 with LiBr/CAN: synthesis of (5-bromo-2,3,4-trimethoxyphenyl)(3,4-dimethoxyphenyl) methanone (9)

To a solution of **6** (332 mg, 1 mmol) and LiBr (96 mg, 1.1 mmol) in CH_3CN (15 mL) was added a solution of CAN (0.60 g, 1.1 mmol) in CH_3CN (15 mL) dropwise at room temperature (rt) and under nitrogen (N_2) over 10 min. After the solution was stirred at rt and under N_2 for 3 days, water (15 mL) was added and the mixture was extracted with EtOAc (2×30 mL). The organic phase was washed with solutions (5%, 2×15 mL) of $NaHCO_3$, water (2×15 mL), and brine (15 mL). Then it was dried over Na_2SO_4 and the solvents were evaporated. Monobromide **9** (401 mg, 97%), the sole product, was crystallized from ethyl acetate/hexane as colorless block crystals. Mp 136–138 °C; R_f (14.3%, EtOAc/hexane) 0.15; δ_H (400 MHz, $CDCl_3$) 7.54 (d, J=2.0 Hz, aromatic, 1H), 7.27 (dd, A part of AB-system, J=2.0, 8.4 Hz, aromatic, 1H), 7.24 (s, aromatic, 1H), 6.85 (d, B part of AB-system, J=8.4 Hz, aromatic, 1H), 3.96 (s, OCH_3, 3H), 3.94 (s, OCH_3, 6H), 3.93 (s, OCH_3, 3H), 3.77 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 192.9 (CO), 154.0 (C), 153.1 (C), 151.9 (C), 149.3 (C), 147.7 (C), 130.9 (C), 130.4 (C), 126.9 (CH), 126.3 (CH), 111.6 (C), 111.1 (C), 110.1 (CH), 62.2 (OCH_3), 61.4 (OCH_3), 61.4 (OCH_3), 56.33 (OCH_3), 56.26 (OCH_3). ν_{max} (CH_2Cl_2, cm^{-1}): 3067, 2934, 2861, 1660, 1593, 1513, 1462, 1415, 1238, 1163, 1147, 1084, 1046, 917; MS m/z (CI, methane) 411.0/413.0 (97/94, M^+). Anal. Calcd for ($C_{18}H_{19}BrO_6$): C 52.57, H 4.66. Found C 52.40, H 4.65.

4.4. Synthesis of (5-bromo-2,3,4-trimethoxyphenyl)(3-bromo-4,5-dimethylphenyl)methanone (10)

This reaction was performed according to standard procedure described in that of **9**. In this reaction, the moles of **6**, CAN and LiBr used were 1.0, 2.2 and 2.2, respectively. After chromatography (SiO_2, 80 g) with EtOAc/hexane (1:6), dibromide **10** (417 mg, 87%, brown liquid), and monobromide **9** (63 mg, 13%) were obtained. R_f (14.3%, EtOAc/hexane) 0.19; *(5-bromo-2,3,4-trimetylphenyl)(3-bromo-4,5-dimetylphenyl)methanone* (**10**): δ_H (400 MHz, $CDCl_3$) 7.43 (s, aromatic, 1H), 6.99 (s, aromatic, 1H), 6.95 (s, aromatic, 1H), 3.94 (s, OCH_3, 3H), 3.88 (s, OCH_3, 3H), 3.83 (s, OCH_3, 3H), 3.82 (s, OCH_3, 3H), 3.64 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 193.0 (CO), 154.9 (C), 153.5 (C), 151.7 (C), 148.4 (C), 147.5 (C), 133.4(C), 129.8 (CH), 128.8 (CH), 116.2 (CH), 113.2 (C), 112.0 (C), 111.7 (C), 61.8 (OCH_3), 61.4 (OCH_3), 61.3 (OCH_3), 56.5 (OCH_3), 56.4 (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 2939, 2842, 1661, 1593, 1506, 1461, 1404, 1376, 1334, 1295, 1261, 1218, 1166, 1094, 1056, 1030, 999, 939; MS m/z (CI, methane) 488.9/490.9/493.0 (51/100/48, M^+). Anal. Calcd for ($C_{18}H_{18}Br_2O_6$): C 44.11, H 3.70. Found C 43.92, H 3.69.

Only, dibromide **10** was obtained when the reaction of **6** (1.0 mmol) with CAN (6.0 mmol) and LiBr (6.0 mmol) was performed according to standard procedure described in that of **9**.

4.5. Reaction of ketone 6 with bromine in different conditions

*4.5.1. Bromination of ketone **6** by 1.1 equiv bromine at rt.* To a stirring solution of ketone **6** (1.0 g, 3.0 mmol, 1 equiv) in $CHCl_3$ (40 mL) was added a solution of bromine (530 mg, 3.3 mmol, 1.1 equiv) in $CHCl_3$ (20 mL) dropwise at rt over 10 min. After the reaction mixture was stirred at rt for 1 day, the solvent was evaporated. Monobromide **9** (401 mg, 96%), the sole product, was crystallized from ethyl acetate/hexane.

*4.5.2. Bromination of ketone **6** by 2.2 equiv bromine at rt.* To a stirred solution of ketone **6** (1.0 g, 3.0 mmol, 1.0 equiv) in $CHCl_3$ (50 mL) was added a solution of bromine (1.06 g, 6.6 mmol, 2.2 equiv) in $CHCl_3$ (10 mL) dropwise at rt over 5 min. The mixture was stirred at the same temperature for 2.5 days, the solvent was evaporated, and chromatography of the residue on silica gel (SiO_2, 110 g) with ethyl acetate/hexane (1:6) gave the dibromide **10** (340 mg, 23%) and monobromide **9** (880 mg, 71%), respectively.

*4.5.3. Bromination of ketone **6** by 6.0 equiv bromine at reflux in $CHCl_3$.* To a stirring solution of ketone **6** (2.0 g, 6.0 mmol) in $CHCl_3$ (50 mL) was added a solution of bromine (36 mmol, 5.77 g, 6.0 equiv) in $CHCl_3$ (20 mL) dropwise at rt over 10 min. After the reaction mixture was stirred and refluxed for 3 days, the reaction mixture was cooled to rt and the solvent was evaporated. The residue was subjected to column chromatography on silica gel (SiO_2, 110 g) and eluted using EtOAc/hexane (1:6) to give the tribromophenol **14** (52 mg, 1.6%), tribromophenol **13** (200 mg, 6%), dibromophenol **12** (1.95 g, 68%), dibromide **10** (472 mg, 20%), and dibromide **11** (55 mg, 1.9%). All products **11**–**14** except for **10** (liquid) were crystallized from ethyl acetate/hexane.

*4.5.4. (2,3-Dibromo-4,5,6-trimethoxyphenyl)(3,4-dimethoxyphenyl) methanone (**11**).* Colorless block crystals; mp 141–143 °C; R_f (14.3%, EtOAc/hexane) 0.14; δ_H (400 MHz, $CDCl_3$) 7.62 (d, 1H, J=1.8 Hz, aromatic, 1H), 7.20 (dd, A part of AB-system, J=1.9 Hz, J=8.4 Hz, aromatic, 1H), 6.84 (d, B part of AB-system, J=8.4 Hz, aromatic, 1H), 3.96 (s, OCH_3, 3H), 3,95 (s, OCH_3, 3H), 3,94 (s, OCH_3, 6H), 3,77 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 191.8 (CO), 154.5 (C), 153.1 (C), 151.0 (C), 149.7 (C), 146.9 (C), 133.1 (C), 129.4 (C), 126.1 (CH), 116.9 (C), 115.7 (C), 110.6 (CH), 110.4 (CH), 62.1 (OCH_3), 61.4 (2 OCH_3), 56.3 (OCH_3), 56.3 (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 2937, 2854, 1665, 1593, 1513, 1460, 1418, 1399, 1296, 1270, 1206, 1164, 1142, 1094, 1021, 999; MS m/z (CI, methane) 488.9/490.9/492.9 (51/100/48, M^+). Anal. Calcd for ($C_{18}H_{18}Br_2O_6$): C 44.11, H 3.70. Found C 44.11, H 3.3.71.

*4.5.5. (5-Bromo-2-hydroxy-3,4-dimethoxyphenyl)(2-bromo-4,5-dimethoxyphenyl)methanone (**12**).* Colorless block crystals; mp 143–146 °C; R_f (14.3%, EtOAc/hexane) 0.35; δ_H (400 MHz, $CDCl_3$) 12.27 (s, OH, 1H), 7.26 (s, aromatic, 1H), 7.11 (s, aromatic, 1H), 6.81 (s, aromatic, 1H), 4.09 (s, OCH_3, 3H), 3.98 (s, OCH_3, 3H), 3.96 (s, OCH_3, 3H), 3,88 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 199.5 (CO), 158.5 (C), 156.6 (C), 151.3 (C), 148.6 (C), 141.8 (C), 131.8 (CH), 130.9 (C), 116.8 (C), 116.1 (CH), 111.7 (CH), 110.5 (C), 106.1 (C), 61.5 (OCH_3), 61.3 (OCH_3), 56.6 (OCH_3), 56.5 (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 3011, 2943, 2837, 2047, 1749, 1631, 1507, 1476, 1442, 1409, 1311, 1261, 1206, 1168, 1108, 1052, 1028, 987, 964, 912; MS m/z (CI, methane) 474.9/476.9/478.9 (51/100/48, M^+). Anal. Calcd for ($C_{17}H_{16}Br_2O_6$): C 42.89, H 3.39. Found C 42.78, H 3.40.

*4.5.6. (5-Bromo-2-hydroxy-3,4-dimethoxyphenyl)(2,3-dibromo-4,5-dimethoxyphenyl)methanone (**13**).* Colorless block crystals; mp 128–130 °C; R_f (14.3%, EtOAc/hexane) 0.42; δ_H (400 MHz, $CDCl_3$) 12.12 (s, OH, 1H), 7.17 (s, 1H), 6.80 (s, aromatic, 1H), 4.09 (s, OCH_3, 3H), 3.97 (s, OCH_3, 3H), 3.94 (s, OCH_3, 3H), 3,87 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 198.7 (CO), 158.6 (C), 156.9 (C), 153.0 (C), 149.4 (C), 141.9 (C), 135.9 (C), 131.3 (CH), 123.2 (C), 116.3 (C), 112.9 (C), 111.19 (CH), 106.5 (C), 61.6 (OCH_3), 61.4 (OCH_3), 60.9 (OCH_3), 56.7 (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 2998, 2940, 2848, 1626, 1545, 1475, 1415, 1373, 1323, 1295, 1256, 1204, 1166, 1127, 1063, 1035, 1002, 968, 915; MS m/z (CI, methane) 552.9/554.9/556.9/558.9 (35/100/97/32, M^+). Anal. Calcd for ($C_{17}H_{15}Br_3O_6$): C 36.79, H 2.72. Found C 36.84, H 2.71.

*4.5.7. (5-Bromo-2-hydroxy-3,4-dimethoxyphenyl)(2,6-dibromo-3,4-dimethoxyphenyl)methanone (**14**).* Pale yellow block crystals; mp 122–125 °C; R_f (14.3%, EtOAc/hexane) 0.47; R_f (14.3%, EtOAc/hexane) 0.47; δ_H (400 MHz, $CDCl_3$) 12.06 (s, OH, 1H), 7.14 (s, aromatic, 1H), 7.10 (s, aromatic, 1H), 4.03 (s, OCH_3, 3H), 3.98 (s, OCH_3, 3H), 3.95, (s, OCH_3, 3H), 3.89 (s, OCH_3, 3H); δ_H (400 MHz, $CDCl_3$) 197.6 (CO), 158.5 (C), 156.8 (C), 154.8 (C), 146.6 (C), 141.9 (C), 132.2 (C), 130.5 (CH), 116.6 (C), 116.3 (CH), 116.0 (C), 114.0 (C), 106.6 (C), 61.5 (OCH_3), 61.4 (OCH_3), 61.0 (OCH_3), 56.7, (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 2937, 2841, 1624, 1580, 1544, 1478, 1445, 1419, 1372, 1320, 1260, 1214, 1125, 1054, 1035, 987, 961; MS m/z (CI, methane) 552.9/554.9/556.9/558.9 (34/100/97/32, M^+). Anal. Calcd for ($C_{17}H_{15}Br_3O_6$): C 36.79, H 2.72. Found C 36.90, H 2.73.

*4.5.8. Bromination of ketone **6** by 10.0 equiv bromine at reflux in $CHCl_3$.* Reaction of ketone **6** (2.0 g, 6.0 mmol) with bromine (60 mmol, 9.6 g, 10.0 equiv) in $CHCl_3$ (50 mL) and separation of the residue were performed according to standard procedure described in 4.4.3. Tribromophenol **14** (68 mg, 2.1%), tribromophenol **13** (367 mg, 11%), dibromophenol **12** (2.12 g, 74%), dibromide **10** (71 mg, 3%), and dibromide **11** (43 mg, 1.5%) were obtained.

4.5.9. Bromination by 10.0 equiv bromine at rt. To a stirred solution of ketone **6** (1.0 g, 3.0 mmol, 1.0 equiv) in $CHCl_3$ (50 mL) was added a solution of bromine (9.64 g, 30.0 mmol, 6.0 equiv) in $CHCl_3$ (10 mL) dropwise at rt over 10 min. The mixture was stirred at the same temperature for 8 days, the solvent was evaporated, and chromatography of the residue on silica gel (SiO_2, 110 g) with EtOAc/hexane (1:6) gave the tribromophenol **14** (40 mg, 2.4%), tribromophenol **13** (217 mg, 13%), dibromophenol **12** (1.05 g, 73%), dibromide **10** (30 mg, 2%), and dibromide **11** (20 mg, 1.4%).

*4.5.10. Standard procedure for bromination of ketone **6** by catalytic Fe at reflux in AcOH for 6 h.* To a stirred at reflux mixture of ketone **6** (1.0 g, 3.0 mmol, 1.0 equiv) and powder Fe (240 mg) in AcOH (50 mL) was added a solution of bromine (5.44 g, 69.0 mmol, 6.0 equiv) in AcOH (10 mL) dropwise at rt over 10 min. The mixture was stirred and heated at reflux for 5 h. After the mixture was cooled to rt and it was poured onto mixture (600 g) of water and ice, the mixture with water was waited for 1 days. Solid was filtered and washed CH_2Cl_2 (300 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated. Chromatography of the residue on silica gel (SiO_2, 90 g) with EtOAc/hexane (1:6) gave known **18** (710 mg, 63%), tetrabromide **16** (380 mg, 19%) and tribromide **15** (120 mg, 7%). The products **15** and **16** were crystallized from ethyl acetate/hexane.

*4.5.11. (2-Bromo-4,5-dimethoxyphenyl)-(2,3-dibromo-4,5,6-trimethoxyphenyl)-methanone (**15**).* Colorless block crystals; mp 102–104 °C; R_f (14.3%, EtOAc/hexane) 0.22; δ_H (400 MHz, $CDCl_3$) 7.39 (s, aromatic, 1H), 7.08 (s, aromatic, 1H), 3.95 (s, OCH_3, 3H), 3.93 (s, OCH_3, 3H), 3.91 (s, OCH_3, 3H), 3.8 (s, OCH_3, 3H), 3.77 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 190.9 (CO), 153.6 (C), 153.3 (C), 151.2 (C), 148.6 (C), 146.9 (C), 133.7 (C), 129.1 (C), 117.4 (C), 117.1 (CH), 116.2 (C), 115.2 (C), 114.9 (CH), 61.9 (OCH_3), 61.5 (OCH_3), 61.3 (OCH_3) 56.6 (OCH_3), 56.5 (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 3006, 2946, 2840, 1649, 1586, 1507, 1455, 1395, 1371, 1342, 1299, 1267, 1205, 1161, 1067, 1090, 1035, 1020, 1002, 936; MS m/z (CI, methane) 566.9/568.9/570.9/572.9 (36/100/94/33, M^+). Anal. Calcd for ($C_{18}H_{17}Br_3O_6$): C 37.99, H 3.01. Found C 37.91, H 3.00.

*4.5.12. (2,3-Dibromo-4,5-dimethoxyphenyl)-(2,3-dibromo-4,5,6-trimethoxyphenyl)-methanone (**16**).* Colorless block crystals; mp 113–115 °C; R_f (14.3%, EtOAc/hexane) 0.33; δ_H (400 MHz, $CDCl_3$) 7.25 (s, aromatic, 1H), 3.94 (s, OCH_3, 3H), 3.91 (s, OCH_3, 3H), 3.90 (s, OCH_3, 3H), 3.85 (s, OCH_3, 3H), 3.72 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 191.5 (CO), 153.9 (C), 152.3 (C), 151.4 (C), 151.1 (C), 146.8 (C), 135.2 (C), 133.1 (C), 124.5 (C), 117.4 (C), 116.5 (C), 116.5 (C), 115.1 (C), 62.0 (OCH_3), 61.5 (OCH_3), 61.3 (OCH_3), 61.0 (OCH_3), 56.6 (OCH_3); ν_{max} (CH_2Cl_2, cm^{-1}): 3077, 2979, 2939, 2844, 1673, 1579, 1554, 1462, 1401, 1304, 1200, 1161, 1105, 1078, 1041, 993, 940, 909; MS m/z (CI, methane) 644.8/646.8/648.8/650.8/652.8 (18/71/100/64/17, M^+). Anal. Calcd for ($C_{18}H_{16}Br_4O_6$): C 33.37, H 2.49. Found C 33.29, H 2.48.

*4.5.13. 1,2,3-Tribromo-4,5-dimethoxybenzene (**18**).* White solid; mp 82–84 °C (lit.[10a] 86 °C); R_f (14.3%, EtOAc/hexane) 0.81; δ_H

(400 MHz, $CDCl_3$) 7.19 (s, aromatic, 1H), 3.86 (s, OCH_3, 3H), 3.83 (s, OCH_3, 3H); δ_C (400 MHz, $CDCl_3$) 153.0 (C), 147.3 (C), 122.4 (C), 119.9 (C), 118.7 (C), 116.6, (CH) 60.8 (OCH_3), 56.7 (OCH_3).

*4.5.14. Bromination of ketone **6** by catalytic Fe at reflux in AcOH for 1.5 h.* This reaction was performed according to the standard procedure described in 4.5.1. To a stirred at reflux mixture of ketone **6** (0.5 g, 1.5 mmol, 1.0 equiv) and powder Fe (120 mg) in AcOH (25 mL) was added a solution of bromine (2.72 g, 38.5 mmol, 6.0 equiv) in AcOH (5 mL) dropwise at rt over 10 min. The mixture was stirred and heated at reflux for 1.5 h. The ^1H NMR spectrum of the reaction mixture was performed and the percent age of compounds **15**, **16**, and **18** was found to be 7, 32, and 61, respectively.

4.6. Crystallography

For the crystal structure determination, a single-crystal of the bromophenols **12**–**16** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatized Mo Kα radiation (λ=0.71073 Å) and oscillation scans technique with $\Delta\omega=5°$ 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 CrystalClear (Rigaku/MSC Inc., 2005) software.[12] The structures were solved by direct methods using SHELXS-97[13] and refined by a full-matrix least-squares procedure using the program SHELXL-97.[13] Hydrogen positions were found from difference Fourier maps and geometric calculations and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data for* **12**: $C_{17}H_{16}O_6Br_2$, crystal system, space group: monoclinic, $P2_1/n$; unit cell dimensions: a=9.458 (2), b=17.685 (3), c=10.523(4) Å, α=90, β=94.35 (3), γ=90°; volume: 1755.04 (2) Å^3; Z=4; calculated density: 1.80 mg/m^3; absorption coefficient: 4.650 mm^{-1}; F(000): 944; θ-range for data collection 2.3–30.6°; refinement method: full-matrix least-square on F^2; data/parameters: 4600/232; goodness-of-fit on F^2: 1.527; final R indices [$I>2\sigma(I)$]: R_1=0.086, wR_2=0.135; R indices (all data): R_1=0.140, wR_2=0.140; largest diff. peak and hole: 0.504 and −0.490 e Å^{-3}; CCDC: 800677. *Crystal data for* **13**: $C_{17}H_{15}O_6Br_3$, crystal system, space group: monoclinic, $P2_1c$; unit cell dimensions: a=12.774 (2), b=12.3020 (3), c=12.8680(4) Å, α=90, β=109.60(3), γ=90°; volume: 1904.9 (4) Å^3; Z=4; calculated density: 1.93 mg/m^3; absorption coefficient: 6.383 mm^{-1}; F(000): 1080; θ-range for data collection 3.2–26.6°; refinement method: full-matrix least-square on F^2; data/parameters: 2200/237; goodness-of-fit on F^2: 1.124; final R indices [$I>2\sigma(I)$]: R_1=0.093, wR_2=0.153; R indices (all data): R_1=0.176, wR_2=0.191; largest diff. peak and hole: 0.992 and −0.902 e Å^{-3}; CCDC: 800857. *Crystal data for* **14**: $C_{17}H_{15}O_6Br_3$, crystal system, space group: triclinic, $P-1$; unit cell dimensions: a=8.6515 (2), b=10.4691 (3), c=11.7338 (4) Å, α=73.71 (3), β=79.35 (3), γ=77.12 (3)° ; volume: 985.89 (4) Å^3; Z=2; calculated density: 1.87 mg/m^3; absorption coefficient: 6.167 mm^{-1}; F(000): 540; θ-range for data collection 2.4–26.4°; refinement method: full-matrix least-square on F^2; data/parameters: 3122/235; goodness-of-fit on F^2: 1.202; final R indices [$I>2\sigma(I)$]: R_1=0.061, wR_2=0.100; R indices (all data): R_1=0.084, wR_2=0.109; largest diff. peak and hole: 0.313 and −0.558 e Å^{-3}; CCDC: 800314. *Crystal data for* **15**: $C_{18}H_{17}O_6Br_3$, crystal system, space group: orthorhombic, $P2_12_12_1$; unit cell dimensions: a=7.7998 (2), b=9.3736 (3), c=27.7532 (4) Å, α=90, β=90, γ=90°; volume: 2029.10 (4) Å^3; Z=4; calculated density: 1.86 mg/m^3; absorption coefficient: 5.995 mm^{-1}; F(000): 1112; θ-range for data collection 2.3–26.4°; refinement method: full-matrix least-square on F^2; data/parameters: 3076/244; goodness-of-fit on F^2: 1.076; final R indices [$I>2\sigma(I)$]: R_1=0.049, wR_2=0.072; R indices (all data): R_1=0.077, wR_2=0.079; largest diff. peak and hole: 0.301 and −0.424 e Å^{-3}; CCDC: 800254. *Crystal data for* **16**: $C_{18}H_{16}O_6Br_4$, crystal system, space group: triclinic, $P-1$; unit cell dimensions: a=9.0333 (2), b=9.5828 (2), c=13.2203 (4) Å, α=73.38 (2), β=74.66 (4), γ=76.03 (4)° ; volume: 1040.44 (5) Å^3; Z=2; calculated density: 2.07 mg/m^3; absorption coefficient: 7.796 mm^{-1}; F(000): 624; θ-range for data collection 2.4–26.4°; refinement method: full-matrix least-square on F^2; data/parameters: 3066/253; goodness-of-fit on F^2: 1.112; final R indices [$I>2\sigma(I)$]: R_1=0.054, wR_2=0.097; R indices (all data): R_1=0.083, wR_2=0.114; largest diff. peak and hole: 0.628 and −0.516 e Å^{-3}; CCDC: 801841.

Acknowledgements

The authors are indebted to the Department of Chemistry and Atatürk University for financial support of this work (Project No.: BAB-2009/84).

References and notes

1. (a) Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353–1395; (b) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335–346; (c) Gribble, G. W. *Environ. Sci. Pollut. Res. Int.* **2000**, *7*, 37–49.
2. (a) Lee, H. S.; Lee, T. H.; Lee, J. H.; Chae, C. S.; Chung, S. C.; Shin, D. S.; Shin, J.; Oh, K. B. *J. Agric. Food Chem.* **2007**, *55*, 6923–6928; (b) Shi, D. Y.; Xu, F.; He, J.; Jing, L.; Li, J.; Fan, X.; Han, L. J. *Chin. Sci. Bull.* **2008**, *53*, 2476–2479.
3. Xu, X.; Song, F.; Wang, S.; Li, S.; Xiao, F.; Zhao, J.; Yang, Y.; Shang, S.; Yang, L.; Shi, J. *J. Nat. Prod.* **2004**, *67*, 1661–1666.
4. Kurata, K.; Taniguchii, K.; Takashima, K.; Hayashi, I.; Suzuki, M. *Phytochemistry* **1997**, *45*, 485–487.
5. (a) Oh, K.-B.; Lee, J. H.; Chung, S. C.; Shin, J.; Shin, H. J.; Kim, H. K.; Lee, H. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 104–108; (b) Xu, N.; Fan, X.; Yan, X.; Li, X.; Niu, R.; Tseng, C. K. *Phytochemistry* **2003**, *62*, 1221–1224.
6. (a) Balaydın, H. T.; Gulcin, I.; Menzek, A.; Goksu, S.; Sahin, E. *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 685–695; (b) Duan, X. J.; Li, X. M.; Wang, B. G. *J. Nat. Prod.* **2007**, *70*, 1210–1213.
7. Wang, W.; Okada, Y.; Shi, H.; Wang, Y.; Okuyama, T. *J. Nat. Prod.* **2005**, *68*, 620–622.
8. (a) Kubo, I.; Ochi, M.; Shibata, K.; Hanke, F. J.; Nakatsu, T.; Tan, K. S. *J. Nat. Prod.* **1990**, *53*, 50–56; (b) Şengül, M. E.; Menzek, A.; Balcı, M. *Turk. J. Chem.* **2006**, *30*, 131–138; (c) Balaydın, H. T.; Akbaba, Y.; Menzek, A.; Şahin, E.; Göksu, S. *Arkivoc* **2009**, *XIV*, 75–87; (d) Akbaba, Y.; Balaydın, H. T.; Göksu, S.; Şahin, E.; Menzek, A. *Helv. Chim. Acta* **2010**, *93*, 1127–1135.
9. Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 6941–6942.
10. (a) Frejka, J.; Sefranek, B. *Collect. Czech. Chem. Commun.* **1936**, *8*, 130–139; (b) Kohn, M.; Steiner, L. *J. Org. Chem.* **1947**, *12*, 30–33.
11. (a) Elix, J. A.; Jiang, H. *Aust. J. Chem.* **1990**, *43*, 1591–1595; (b) Sharghi, H.; Tamaddon, F. *Tetrahedron* **1996**, *52*, 13623–13640; (c) Liu, T.; Huazhou Ying, H.; Lin, G.; Hu, Y. *Synth. Commun.* **2008**, *38*, 1815–1821.
12. Rigaku/MSC, 9009 new Trails Drive, The Woodlands, TX 77381.
13. Sheldrick, G. M. *SHELXS97 and SHELXL97*; University of Göttingen: Germany, 1997.