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# Synthesis and antimicrobial activities of halogenated bis(hydroxyphenyl)methanes

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ABSTRACT

A series of halophenols was prepared by the reaction of bis(hydroxyphenyl)methanes with effective halogenating agents such as bromine and sulfuryl chloride. One of these compounds, a biologically active halophenol—2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**1**)—frequently isolated from red algae, was synthesized for the first time. Other halophenols included several novel compounds, together with known derivatives that were synthesized from the phenolic intermediates, bis(3,4-dihydroxyphenyl)methane (**5**) and bis(2-hydroxyphenyl)methane (**14**). All of the synthesized compounds were tested for antimicrobial activity against Gram-positive, Gram-negative bacteria and fungi. The preliminary structure–activity relationship was investigated in order to determine the essential structural requirements for their antimicrobial activity. Of all these halophenols, 2,2′,3,3′,6-pentabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**8**) was found to be the most active against *Candida albicans*, *Aspergillus fumigatus*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes* while 3,3′,5,5′-tetrachloro-2,2′-dihydroxydiphenylmethane (**18**) exerted a powerful antibacterial effect against *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Proteus vulgaris*, and *Salmonella typhimurium*.



Bromophenol compounds frequently isolated from various marine red algae,[1–5] have been reported to exhibit a wide spectrum of pharmacological activities including antibacterial[4] and antimicrobial[5] activities. We recently reported the isolation and synthesis of some of these bromophenol derivatives and their antimicrobial activities.[3] Among natural bromophenols, 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**1**) was found to be the most active against various fungi, whereas a synthetic bromophenol—3,3′,5,5′-tetrabromo-2,2′-dihydroxydiphenylmethane (**2**)—showed a powerful antibacterial effect against Gram-negative and Gram-positive bacteria (Fig. 1).

Additionally, compound **1** exhibited potent isocitrate lyase (ICL) inhibitory activity and protected rice plants from *Magnaporthe grisea* infection.[6] Due to these interesting bioactivities, we decided to develop a synthetic strategy which would allow us to produce not only the natural bromophenol, but also its analogues. In this paper, we describe the synthesis and antimicrobial activity of some halophenols and their structure–activity relationship.

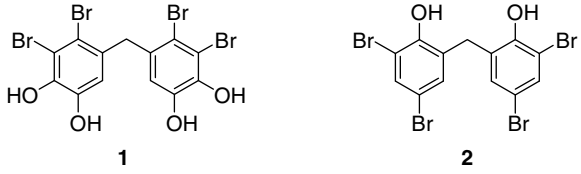


**Figure 1.** Bioactive bromophenols.

In our previous study,[3] we reported the synthesis of bis(3,4-dihydroxydiphenyl)methane (**5**) from bromophenol **1** by a catalytic hydrodehalogenation reaction, in which **5** could be utilized as a common building block in the synthesis of **1** and its analogues.

We thus undertook the synthesis of bioactive bromophenol **1** via compound **5** as shown in Scheme 1. Compound **3** was obtained by the sequential treatment of 4-bromo-1,2-(methylenedioxy)benzene with *n*-butyllithium and 3,4-(methylenedioxy)benzaldehyde with a 79% yield. Subsequently, the reductive removal of the benzylic alcohol under standard hydrogenation conditions in the presence of a catalytic amount of $Pd(OH)_2$ afforded bis(3,4-methylenedioxyphenyl)methane (**4**)[7] with a 51% yield. Deprotection of

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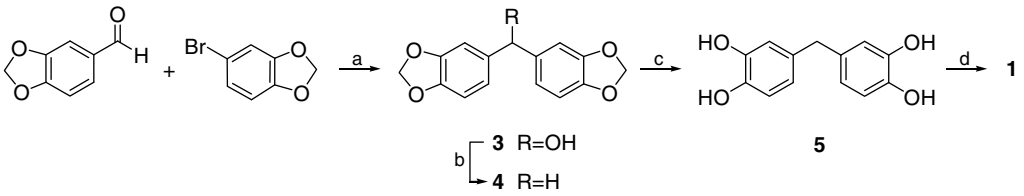



**Scheme 1.** Reagents and conditions: (a) *n*-BuLi, THF, −78 °C to rt; (b) $H_2$, $Pd(OH)_2$/C, MeOH/THF, rt; (c) $BBr_3$, $CH_2Cl_2$, rt; (d) excess $Br_2$, AcOH, rt.

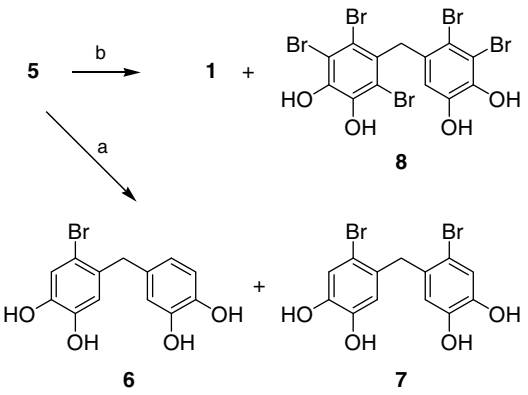
the two methylene groups in **4** with $BBr_3$ yielded 64% of the phenolic compound **5** and the treatment of compound **5** with excess bromine in acetic acid resulted in a 57% conversion to bioactive bromophenol **1**.

In the course of our research to enhance the spectrum and potency of bromophenols, we embarked on the synthesis and bioactivity test of the relatively less explored halophenol derivatives of compound **5**.

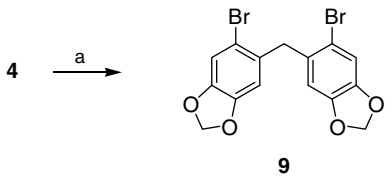
With this purpose, we directed our efforts to investigate the changes of antibacterial activity resulting from the number and position of bromine atoms attached to the phenol ring. Therefore the analogues 2-bromo-3′,4,4′,5-tetrahydroxydiphenylmethane (**6**), 2,2′-dibromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**7**) and 2,2′,3,3′,6-pentabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**8**) were synthesized by the reaction of phenolic compound **5** with bromine as illustrated in Scheme 2.[8]

In order to examine the relationship between biological activity and free hydroxyl groups in aromatic rings, bis(2-bromo-4,5-methylenedioxyphenyl)methane (**9**), a form of **7** in which hydroxyl groups are protected, was also prepared from compound **4** with an 87% yield (Scheme 3).[9]

The in vitro antimicrobial activities of the new bromophenols **6**–**9** together with bioactive compounds **1** and **2** were assessed against three representative Gram-positive bacteria viz. *Staphylococcus aureus* (ATCC 6538p), *Bacillus subtilis* (ATCC 6633), and *Micrococcus luteus* (IFC 12708), three Gram-negative bacteria viz. *Proteus vulgaris* (ATCC 3851), *Salmonella typhimurium* (ATCC 14028), and *Escherichia coli* (ATCC 25922), and four fungi viz. *Candida albicans* (ATCC 10231), *Aspergillus fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185), and *Trichophyton mentagrophytes* (IFO 40996).[10,11] The minimum inhibitory concentrations (MICs) of the compounds are displayed in Tables 1 and 2. Among the three bromophenols, the multi-brominated phenolic compounds **7** and **8** exhibited moderate inhibition activity against all tested Gram-positive and Gram-negative organisms except *E. coli*, whereas compounds **6** and **9** showed no antibacterial activity whatsoever (Table 1). However, the activity of compound **8** was especially interesting,




**Scheme 2.** Reagents and conditions: (a) $Br_2$, $CH_2Cl_2$/AcOH, rt; (b) excess $Br_2$, AcOH, 50 °C.




**Scheme 3.** Reagent: (a) excess $Br_2$, AcOH.

**Table 1**
Antibacterial activity

| Compound | Antibacterial activity (MIC, μg/ml) | | | | | |
|---|---|---|---|---|---|---|
| | *S. aureus* | *B. subtilis* | *M. luteus* | *P. vulgaris* | *S. typhimurium* | *E. coli* |
| **1** | 25 | 25 | 25 | 25 | 25 | 50 |
| **2** | 1.56 | 1.56 | 1.56 | 1.56 | 3.12 | >100 |
| **6** | >100 | >100 | 100 | >100 | >100 | >100 |
| **7** | 25 | 25 | 12.5 | 25 | 25 | >100 |
| **8** | 25 | 25 | 25 | 12.5 | 25 | 50 |
| **9** | >100 | >100 | >100 | >100 | >100 | >100 |
| **10** | >100 | >100 | 100 | >100 | >100 | >100 |
| **11** | 50 | 50 | 25 | 50 | 50 | >100 |
| **12** | 12.5 | 25 | 12.5 | 25 | 25 | 100 |
| **13** | 25 | 25 | 25 | 25 | 25 | 50 |
| **15** | 50 | 100 | 50 | 100 | 100 | 100 |
| **16** | 25 | 25 | 25 | 25 | 25 | 50 |
| **17** | 12.5 | 12.5 | 12.5 | 12.5 | 6.25 | 100 |
| **18** | 0.78 | 1.56 | 0.78 | 0.78 | 3.12 | >100 |
| Ampicillin | 1.56 | 1.56 | 1.56 | 3.12 | 3.12 | 12.5 |

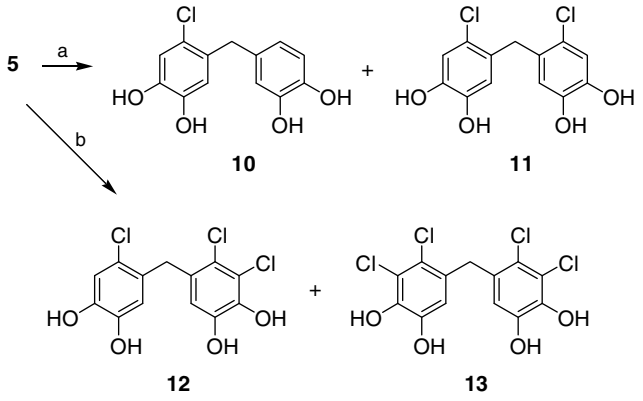
*Microorganisms: Staphylococcus aureus* ATCC 6538p; *Bacillus subtilis* ATCC 6633; *Micrococcus luteus* IFC 12708; *Proteus vulgaris* ATCC 3851; *Salmonella typhimurium* ATCC 14028; *Escherichia coli* ATCC 25922.

**Table 2**
Antifungal activity

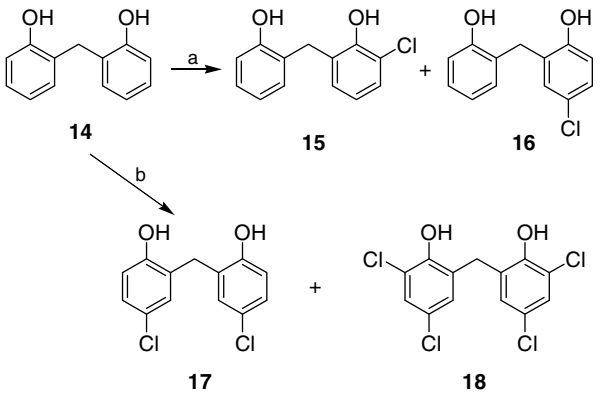
| Compound | Antifungal activity (MIC, μg/ml) | | | |
|---|---|---|---|---|
| | *C. albicans* | *A. fumigatus* | *T. rubrum* | *T. mentagrophytes* |
| **1** | 25 | 12.5 | 12.5 | 1.56 |
| **2** | >100 | >100 | >100 | >100 |
| **6** | >100 | >100 | >100 | >100 |
| **7** | >100 | >100 | >100 | 50 |
| **8** | 6.25 | 3.12 | 1.56 | 1.56 |
| **9** | >100 | >100 | >100 | >100 |
| **10** | >100 | >100 | >100 | >100 |
| **11** | >100 | >100 | >100 | 50 |
| **12** | 100 | >100 | >100 | 25 |
| **13** | 50 | 50 | 50 | 3.12 |
| **15** | 50 | 100 | 100 | 12.5 |
| **16** | 50 | 50 | 50 | 6.25 |
| **17** | 25 | 50 | 50 | 12.5 |
| **18** | 100 | >100 | >100 | 12.5 |
| Amphotericin B | 6.25 | 3.12 | 3.12 | 3.12 |

*Microorganisms: Candida albicans* ATCC 10231; *Aspergillus fumigatus* HIC 6094; *Trichophyton rubrum* IFO 9185; *Trichophyton mentagrophytes* IFO 40996.

exhibiting MIC values against *C. albicans*, *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* some twofold times lower than the reference compound, amphotericin B (Table 2). These results revealed




**Scheme 4.** Reagents: (a) $SO_2Cl_2$, AcOH/$CH_2Cl_2$; (b) excess $SO_2Cl_2$, AcOH.




**Scheme 5.** Reagents: (a) $SO_2Cl_2$, AcOH/$CH_2Cl_2$; (b) excess $SO_2Cl_2$, AcOH.

that the presence of free hydroxyl groups and two or more bromine atoms attached to the phenol ring are important for antimicrobial activity.

The study continued, focused now on establishing whether the type of substituting halogen, specifically chlorine, could alter the potency of the antimicrobial activity of the halophenols. These halophenol analogues have been synthesized as shown in Schemes 4 and 5.

To investigate the effect on the antimicrobial activity resulting from the different positions and number of chlorine atoms attached to the phenol ring, several chlorinated analogues were synthesized by reaction of **5** with sulfuryl chloride (Scheme 4). The resulting compounds were identified as 2-chloro-3′,4,4′,5-tetrahydroxydiphenylmethane (**10**), 2,2′-dichloro-4,4′,5,5′-tetrahydroxydiphenyl methane (**11**), 2,2′,3-trichloro-4,4′,5,5′-tetrahydroxydiphenylmethane (**12**), and 2,2′,3,3′-tetrachloro-4,4′,5,5′-tetrahydroxydiphenylmethane (**13**).[12]

In order to examine the bioactivities of analogues of the potent antibacterial bromophenol **2**, similar chlorophenols were prepared from commercially available bis(2-hydroxyphenyl)methane (**14**). Treatment of compound **14** with two equivalents of sulfuryl chloride in acetic acid:$CH_2Cl_2$ (1:1) yielded a mixture of chlorophenols, consisting of 38% of 3-chloro-2,2′-dihydroxydiphenylmethane (**15**)[14] and 51% of 3-chloro-2′,6-dihydroxydiphenylmethane (**16**).[15] Similarly, two well known chlorophenols—3,3′-dichloro-6,6′-dihydroxydiphenylmethane (**17**)[16] and 3,3′,5,5′-tetrachloro-2,2′-dihydroxydiphenylmethane (**18**)[17]—were prepared from the reaction of compound **14** with excess sulfuryl chloride in the acetic acid yielding 9% and 58%, respectively (Scheme 5).

Antibacterial and antifungal activity in vitro testing was performed on the eight chlorophenols **10**–**13** and **15**–**18** prepared as described above. Results expressed as minimum inhibitory concentrations are listed in Tables 1 and 2. As can be appreciated, monochlorinated compound **10** resulted to be almost inactive against all Gram-negative, Gram-positive bacteria and fungi tested. These results were similar to those obtained with the mono-brominated compound **6**.

In terms of antibacterial activity, chlorophenol **18** exhibited roughly twofold lower MIC values against *S. aureus*, *B. subtilis*, *M. luteus*, *P. vulgaris*, and *S. typhimurium* as compared to the reference compound, ampicillin. It was interesting that *E. coli* was resistant towards compound **18**. Conversely, the other multi-chlorinated chlorophenols **11**–**13** and **17** revealed only moderate to weak activity against various bacteria with the exception of *E. coli* (Table 1).

In summary, a number of halophenols were prepared and their antimicrobial activity tested against various Gram-positive, Gram-negative bacteria and fungi. Among these, one of them—2,2′,3,3′,6-pentabromo-4,4′,5,5′-tetrahydroxydiphenylmethane (**8**)—displayed the highest activity against *C. albicans*, *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* while another chlorophenol—3,3′,5,5′-tetrachloro-2,2′-dihydroxydiphenylmethane (**18**)—showed a potent antibacterial effect against *S. aureus*, *B. subtilis*, *M. luteus*, *P. vulgaris*, and *S. typhimurium*. By modifying the naturally occurring product, bromophenol, we were thus able to obtain several compounds which showed promising potency profiles in antimicrobial assays.

## Acknowledgments

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8. *Experimental:* The 1D and 2D NMR spectra were obtained at 500 and 125 MHz for $^1H$ and $^{13}C$, respectively, on a Varian UNITY 500 spectrometer in methanol-$d_4$ with solvent peaks as references. Mass spectra were recorded on a ThermoFinnigan Surveyor MSQ spectrometer. Column chromatography was performed with silica gel (230–400 mesh), RP-18 reversed-phase silica gel (43–60 μm).*General procedure:* A mixture of bis(3,4-dihydroxydiphenyl)methane (**5**) (24 mg, 0.10 mmol) of and bromine (31 mg, 0.24 mmol) in a mixture of acetic acid and dichloromethane (2 ml, 1:1) was stirred at room temperature for 2 h. The excess of bromine was removed by blowing with $N_2$, and the solvent was evaporated under reduced pressure. The crude products were purified by reversed-phase HPLC (YMC ODS-A column, 1 cm × 25 cm, 40% aq $CH_3OH$) to give 6.5 mg (21%) and 18 mg (46%) of bromophenols **6** and **7**, respectively.
*2-Bromo-3′,4,4′,5-tetrahydroxydiphenylmethane* (**6**): $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 6.92 (1H, s, H-3), 6.66 (1H, d, $J$ = 7.80 Hz, H-5′), 6.57 (1H, d, $J$ = 1.95 Hz, H-2′), 6.56 (1H, s, H-6), 6.48 (1H, dd, $J$ = 7.80, 1.95 Hz, H-6′), 3.76 (2H, s, $CH_2$); $^{13}C$ NMR ($CD_3OD$, 125 MHz) $\delta$ 146.1, 146.0, 145.6, 144.4, 133.3, 133.2, 121.2, 119.9, 118.5, 117.0, 116.2, 113.5, 41.1; APCI(−) $m/z$ 309 (M−H).
*2,2′-Dibromo-4,4′,5,5′-tetrahydroxydiphenylmethane* (**7**): $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 6.97 (2H, s, H-3, H-3′), 6.45 (2H, s, H-6, H-6′), 3.83 (2H, s, $CH_2$); $^{13}C$ NMR ($CD_3OD$, 125 MHz) $\delta$ 146.0 (2×), 145.8 (2×), 131.6 (2×), 120.0 (2×), 118.2 (2×), 113.8 (2×), 41.3; APCI(−) $m/z$ 387 (M−H).
Reacting 21 mg of **5** with 124 mg of bromine at 50 °C for 6 h yielded 22 mg (45%) and 11 mg (19%) of bromophenols **1** and **8**, respectively.
*2,2′,3,3′,6-Pentabromo-4,4′,5,5′-tetrahydroxydiphenylmethane* (**8**): $^1H$ NMR ($CD_3OD$, 500 MHz) $\delta$ 6.04 (1H, s, H-6′), 4.37 (2H, s, $CH_2$); $^{13}C$ NMR ($CD_3OD$,

125 MHz) $\delta$ 146.3, 145.5, 145.2, 144.0, 131.9, 131.0, 118.4, 116.3, 114.6, 114.5, 114.35, 114.32, 46.6; APCI(−) *m/z* 626 (M−H).

9. *Bis(2-bromo-4,5-methylenedioxyphenyl)methane* (**9**): $^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 7.06 (2H, s, H-3, H-3′), 6.49 (2H, s, H-6, H-6′), 5.95 (4H, s, $2CH_2$), 3.97 (2H, s, $CH_2$); $^{13}$C NMR ($CD_3OD$, 125 MHz) $\delta$ 149.1 (2×), 148.7 (2×), 133.3 (2×), 115.7 (2×), 113.5 (2×), 111.1 (2×), 103.2 (2×), 42.5; APCI(−) *m/z* 411 (M−H).
10. Three Gram-positive bacteria (*Staphylococcus aureus* ATCC 6538p, *Bacillus subtilis* ATCC 6633, and *Micrococcus luteus* IFO 12708) and three Gram-negative bacteria (*Proteus vulgaris* ATCC 3851, *Salmonella typhimurium* ATCC 14028, and *Escherichia coli* ATCC 35218) were used for antimicrobial activity tests. Bacteria were grown overnight in Luria Bertani (LB) broth at 37 °C, harvested by centrifugation, and then washed twice with sterile distilled water. Stock solutions of the series compound were prepared in DMSO. Each stock solution was diluted with Standard method broth (Difco) to prepare serial twofold dilutions in the range of 100–0.78 μg/ml. Ten microliters of the broth containing approximately $10^5$ colony-forming units (cfu)/ml of test bacteria were added to each well of a 96-well microtiter plate. Culture plates were incubated for 24 h at 37 °C.
11. *Candida albicans* ATCC 10231, *Aspergillus fumigatus* HIC 6094, *Trichophyton rubrum* IFO 9185, and *Trichophyton mentagrophytes* IFO 40996 were used for antifungal activity tests. *C. albicans* was grown for 48 h at 28 °C in YPD broth (1% yeast extract, 2% peptone, and 2% dextrose), harvested by centrifugation, and then washed twice with sterile distilled water. *A. fumigatus*, *T. rubrum*, *and T. mentagrophytes* were plated in potato dextrose agar (PDA) (Difco), incubated at 28 °C for 2 weeks. Spores were washed three times with sterile distilled water and resuspended in distilled water to obtain an initial inoculum size of $10^5$ spores/ml. Each test compound was dissolved in DMSO and diluted with potato dextrose broth (Difco) to prepare serial twofold dilutions in the range of 100–0.8 μg/ml. Ten microliters of the broth containing about $10^3$ (for yeast) and $10^4$ (for filamentous fungi) cells/ml of test fungi was added to each well of a 96-well microtiter plate. Culture plates were incubated for 48–72 h at 28 °C.
12. The reaction of 28 mg (0.12 mmol) of **5** with 29 mg (0.21 mmol) of sulfuryl chloride in an ice bath for 2 h yielded 15 mg (47%) and 6 mg (17%) of chlorophenols **10** and **11**,[13] respectively.
*2-Chloro-3′,4,4′,5-tetrahydroxydiphenylmethane* (**10**): $^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 6.75 (1H, s, H-3), 6.66 (1H, d, $J$ = 7.80 Hz, H-5′), 6.57 (1H, d, $J$ = 1.95 Hz, H-2′), 6.54 (1H, s, H-6), 6.48 (1H, dd, $J$ = 7.80, 1.95 Hz, H-6′), 3.75 (2H, s, $CH_2$); $^{13}$C NMR ($CD_3OD$, 125 MHz) $\delta$ 146.1, 145.5, 145.4, 144.4, 133.3, 131.4, 124.2, 121.2, 118.4, 117.0, 116.8, 116.2, 38.6; ESI(−) 265 *m/z* (M−H)
The reaction of 33 mg (0.14 mmol) of **5** with 130 mg (0.96 mmol) of sulfuryl chloride in an ice bath for 4 h gave 27 mg (58%) and 10 mg (19%) of chlorophenols **12** and **13**, respectively.
*2,2′,3-Trichloro-4,4′,5,5′-tetrahydroxydiphenylmethane* (**12**): $^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 6.79 (1H, s, H-3′), 6.46 (1H, s, H-6′), 6.42 (1H, s, H-6), 3.89 (2H, s, $CH_2$); $^{13}$C NMR ($CD_3OD$, 125 MHz) $\delta$ 146.0, 145.9, 145.6, 142.9, 130.7, 129.1, 124.6, 123.2, 120.9, 118.1, 117.0, 115.9, 37.1; ESI(−) *m/z* 334 (M−H).
*2,2′,3,3′-Tetrachloro-4,4′,5,5′-tetrahydroxydiphenylmethane* (**13**): $^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 6.42 (2H, s, H-6, H-6′), 3.95 (2H, s, $CH_2$); $^{13}$C NMR ($CD_3OD$, 125 MHz) $\delta$ 146.1 (2×), 143.2 (2×), 130.0 (2×), 123.3 (2×), 121.0 (2×), 115.8 (2×), 38.1; ESI(−) *m/z* 369 (M−H).
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17. Commercially available **18** can be purchased from Pfaltz & Bauer, Inc.