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AN ATTEMPT FOR BIARYL COUPLING REACTION OF BENZYL BENZOATE DERIVATIVES UNDER ULLMANN CONDITIONS

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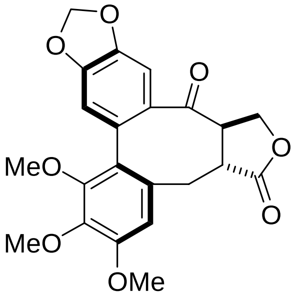
Abstract – The biaryl coupling reaction of benzyl benzoate derivatives (**3**) and (**4**) was examined with copper(0) reagent. A dimerized product (**9**) was mainly obtained whereas the desired intramolecularly coupled product (**11**) was not detected when **3** was employed as the substrate. On the other hand, the reaction of **4** afforded a small amount of the desired lactone (**14**) although the main product was the dimerized **12**.

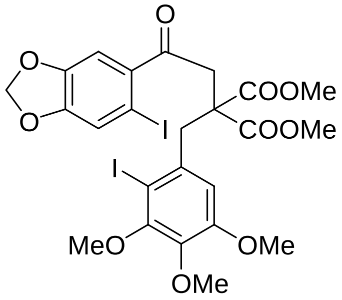
Unsymmetrical 2,2'-disubstituted biaryl compounds attract much attention because several natural products having such moieties exhibit biologically interesting activities. For example, steganone (**1**) has been known to be an antileukaemic lignan lactone.[1] For the construction of a biaryl moiety in the steganone synthesis, photocyclization[2] or the oxidative biaryl coupling reaction[3] has usually been employed. The Suzuki coupling,[4] S_NAr reaction,[5] and [2+2+2] three-component cyclization reaction[6] were also reported as effective methods for the formation of the biaryl part in the steganone synthesis.[7]

The Ullmann coupling reaction[8] is a conventional technique for the synthesis of biaryl compounds.[9] However, this method is not effective for unsymmetrical biaryl compounds because a competitive homo-coupling that produces a symmetrically coupled product cannot be avoided. In fact, Ziegler reported that the intramolecular Ullmann reaction of bisiodide (**2**) failed because the homo-coupling or dehalogenation was predominantly observed.[10] In 1993, Takahashi *et al.* reported the successful Ullmann coupling of linker-incorporated bisbenzoates to form unsymmetrical biaryl compounds.[11]

On the other hand, we postulated that benzyl benzoates would be good precursors for the intramolecular Ullmann coupling reaction in order to obtain the 7*H*-dibenzo[*c*,*e*]oxepin-5-one derivatives. In this article, we describe an attempt for the biaryl coupling reaction of the benzyl benzoate derivatives.



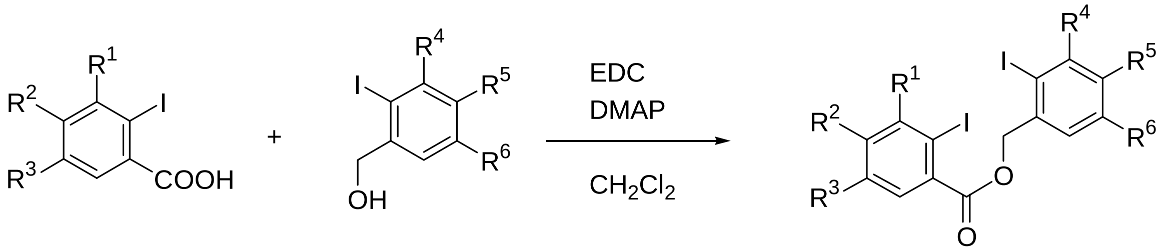
1: (-)-Steganone



2

The benzyl benzoates (**3**) and (**4**) were easily prepared *via* esterification between the corresponding 2-iodobenzoic acids (**5**) and (**6**), and 2-iodobenzyl alcohols (**7**) and (**8**), respectively (Scheme 1). These substrates were examined for the intramolecular Ullmann coupling reactions.

Scheme 1



5: R^1 = H; R^2, R^3 = $-OCH_2O-$
6: R^1 = R^2 = R^3 = -OMe

7: R^4 = R^5 = R^6 = -OMe
8: R^4 = H; R^5, R^6 = $-OCH_2O-$

3: R^1 = H; R^2, R^3 = $-OCH_2O-$
R^4 = R^5 = R^6 = -OMe
4: R^1 = R^2 = R^3 = -OMe
R^4 = H; R^5, R^6 = $-OCH_2O-$

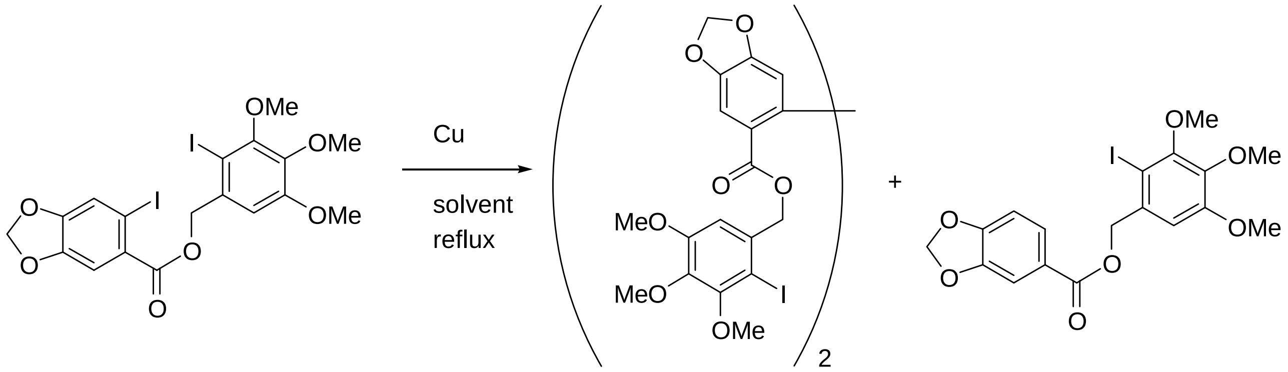
As shown in Table 1, benzyl benzoate (**3**) did not produce the desired lactone (**11**) whereas the dimerized product (**9**) and dehalogenated ester (**10**) were produced when DMF (dimethylformamide) or DMA (dimethylacetamide) was used as the reaction medium. DMSO (dimethyl sulfoxide) and mesitylene were not suitable for this reaction thus no isolatable products were obtained.

On the other hand, the reaction of the ester (**4**) with copper in refluxing DMF produced almost a similar result to that above, in which the dimerized biaryl compound (**12**) and dehalogenated ester (**13**) were obtained. In this case, however, the desired lactone (**14**) was fortunately isolated although the yield was quite low.

In order to confirm the structures of the dimers (**9**) and (**12**), degradation experiments were carried out. The treatment of **9** with DIBAL afforded bisbenzyl alcohol (**15**) along with **7**. When the similar transformation of **12** was examined, the expected bis benzyl alcohol (**16**) was obtained as the main product.

Although the intramolecular Ullmann coupling reactions of benzyl benzoate-type substrates (**3**) and (**4**) were not successful, a small amount of 7*H*-dibenzo[*c*,*e*]oxepin-5-one (**14**) was isolated from the reaction of **4**. We are now in the process of improving the preparation of the unsymmetrical 2,2'-disubstituted biaryl compounds.

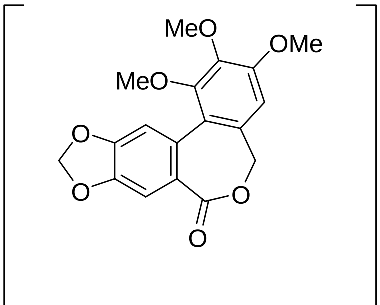
Table 1. Reaction of **3** under Ullmann conditions



3 **9** **10**

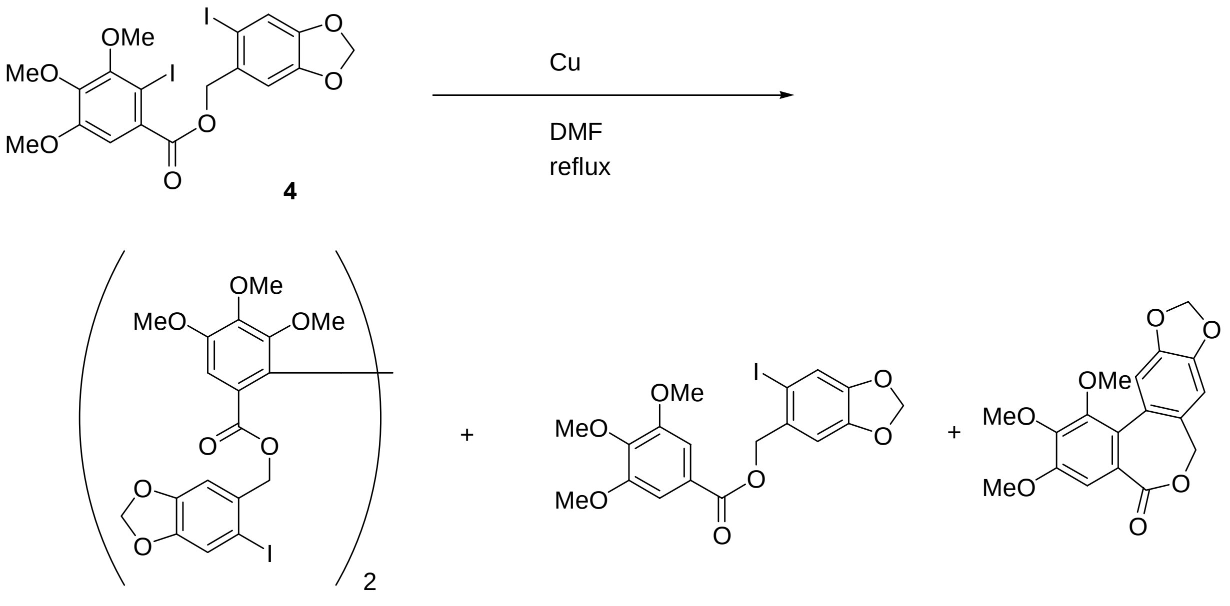
Run	solvent	time (h)	yield (%) 9	yield (%) 10
1	DMF	2	52	16
2	DMA	2	25	49
3	DMSO	1	–[a]	
4	mesitylene	8	trace	–[b]

a) Many spots on TLC. *b*) Not detected.



11

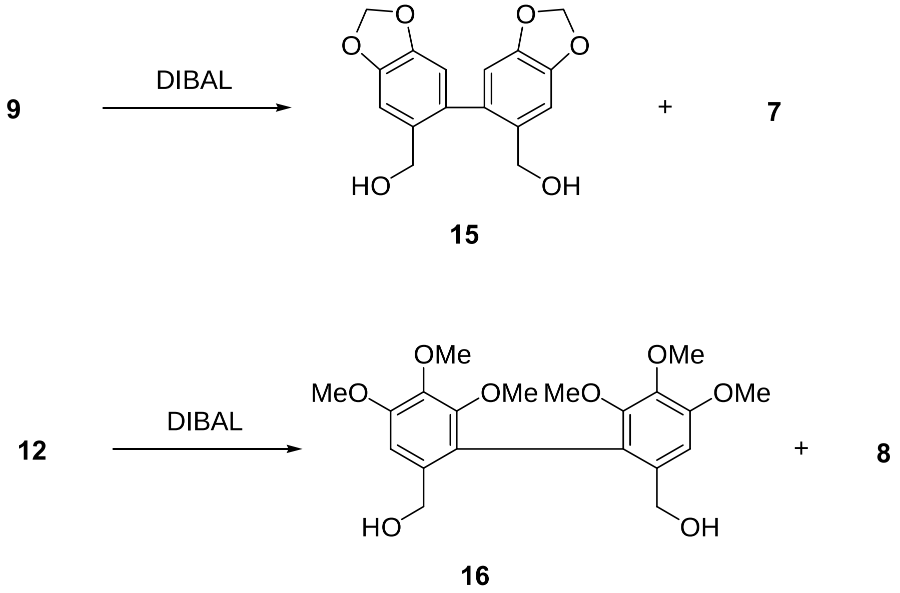
Scheme 2



4

12 (62%) **13** (25%) **14** (5%)

Scheme 3



EXPERIMENTAL

General: Melting points were measured using a Yanagimoto micro melting point hot-plate apparatus and are uncorrected. IR spectra were recorded on a FTIR-350 spectrophotometer. NMR spectra were taken with a Varian VXR-500 or VXR-200 instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. FAB-MS was obtained with a VG-70SE instrument using *m*-nitrobenzyl alcohol as the matrix. Silica gel column chromatography was carried out using a Wako-gel C-200. Merck Silica-gel 60 F254 plates (No. 5744) were used for the preparative TLC. All reactions were carried out under an argon atmosphere.

Substrates: 6-Iodopiperonylic acid (**5**),[12] 2-iodo-3,4,5-trimethoxybenzoic acid (**6**),[13] 2-iodo-3,4,5-trimethoxybenzyl alcohol (**7**),[10] and 6-iodopiperonyl alcohol (**8**)[14] are known compounds. Copper was purified by a published method.[15]

2-Iodo-3,4,5-trimethoxybenzyl 6-iodo-1,3-benzodioxole-5-carboxylate (3)

To a solution of **5** (2.80 g, 9.59 mmol) and **7** (1.82 g, 5.62 mmol) in CH_2Cl_2 (methanol free, 100 mL), EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 1.89 g, 9.86 mmol) and DMAP (*N*, *N*-dimethylaminopyridine, 145 mg, 1.19 mmol) were successively added. The mixture was stirred for 3 h at rt, washed with water and brine, and dried over magnesium sulfate. After evaporation, the resulting solid was recrystallized from CH_2Cl_2 - Et_2O to give colorless needles (2.67 g, 79%), mp 102—104℃. IR (KBr) cm^{-1} : 2940, 1730, 1480, 1380, 1240, 1135, 1030, 1000. ^1H-NMR (500 MHz, $CDCl_3$) δ: 3.87 (3H, s), 3.88 (3H, s), 3.90 (3H, s), 5.35 (2H, s), 6.04 (2H, s), 6.92 (1H, s), 7.42 (1H, s), 7.45 (1H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 56.25, 60.78, 60.93, 71.09, 85.16, 86.80, 102.40, 109.84, 111.23, 120.91, 127.00, 133.52, 142.09, 148.06, 151.19, 153.32, 153.68, 164.87. *Anal*. Calcd for $C_{18}H_{15}O_8I$: C, 36.14; H, 2.70. Found: C, 36.02; H, 2.85.

6-Iodo-1,3-benzodioxol-5-ylmethyl 2-iodo-3,4,5-trimethoxybenzoate (**4**)

To a solution of **6** (3.95 g, 11.7 mmol) and **8** (2.50 g, 8.99 mmol) in CH_2Cl_2 (methanol free, 100 mL), EDC (2.76 g, 14.4 mmol) and DMAP (176 mg, 1.44 mmol) were successively added. After 2 h, **6** (608 mg, 1.80 mmol) and EDC (517 mg, 2.70 mmol) were added again to the mixture because it was found that **8** still remained based on a TLC analysis. The mixture was stirred for 1 h at rt, washed with water and brine, and dried over magnesium sulfate. After evaporation, the resulting residue was subjected to silica gel column chromatography with AcOEt-hexane (1:2) that produced a colorless solid which was recrystallized from hexane - Et_2O. Colorless needles of **4** (4.32 g, 80%) were obtained in pure form, mp 125—126°C (Et_2O-hexane). IR (KBr) cm^{-1} : 2940, 1735, 1480, 1380, 1330, 1240, 1215, 1100, 1040, 1010, 925, 865. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.87 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 5.30 (2H, s), 5.99 (2H, s), 7.05 (1H, s), 7.30 (2H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 56.28, 60.80, 61.01, 71.05, 84.13, 87.49, 101.86, 110.76, 110.89, 118.82, 130.36, 131.26, 145.00, 148.39, 148.60, 153.27, 153.84, 165.89. FAB-MS (positive ion mode) m/z : 598 $[M]^+$. *Anal.* Calcd for $C_{18}H_{16}O_7I_2$: C, 36.14; H, 2.70. Found: C, 36.40; H, 2.76.

Typical Procedure for Ullmann Coupling Reaction (**Table 1, Run 1**)

A mixture of Cu (170 mg, 2.68 mmol) and DMF (2 mL) was refluxed for 30 min. A solution of **3** (200 mg, 0.334 mmol) in DMF (2 mL) was added *via* syringe and the mixture was refluxed for 2 h. After cooling, the mixture was filtered and diluted with ether. The solution was successively washed with 28% aqueous ammonia solution, water, and brine. After evaporation, the resulting oil was subjected to silica gel column chromatography with ether - chloroform (1:100) to produce **9** (81.6 mg, 52%) and **10** (24.4 mg, 16%).

6,6'-Bis(2-Iodo-3,4,5-trimethoxybenzyl 1,3-benzodioxole-5-carboxylate) (**9**)

Colorless prisms mp 150.5—152.5°C (CH_2Cl_2-Et_2O). IR (KBr) cm^{-1} : 2950, 1690, 1480, 1330, 1255, 1105, 1035, 1000. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.85 (6H, s), 3.89 (6H, s), 3.91 (6H, s), 4.99 (2H, d, *J* = 12.0), 5.09 (2H, d, *J* = 12.0), 5.98 (2H, d, *J* = 1.4), 6.00 (2H, d, *J* = 1.4), 6.49 (2H, s), 6.64 (2H, s), 7.30 (2H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 30.88, 56.14, 60.70, 60.90, 70.70, 87.66, 101.99, 109.56, 110.01, 121.91, 133.46, 139.60, 141.98, 146.36, 150.13, 153.03, 153.39, 165.53. *Anal.* Calcd for $C_{36}H_{32}O_{14}I_2$: C, 45.88; H, 3.42. Found: C, 46.05; H, 3.37.

2-Iodo-3,4,5-trimethoxybenzyl 1,3-benzodioxole-5-carboxylate (**10**)

Colorless prisms, mp 120—122°C (CH_2Cl_2-hexane). IR (KBr) cm^{-1} : 2910, 1705, 1500, 1330, 1280, 1260, 1105, 765. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.85 (3H, s), 3.87 (3H, s), 3.89 (3H, s), 5.32 (2H, s), 6.03 (2H, s), 6.83 (1H, d, *J* = 8.2), 6.88 (1H, s), 7.50 (1H, d, *J* = 1.7), 7.70 (1H, dd, *J* = 8.2, 1.7). ^{13}C-NMR (125 Hz, $CDCl_3$) δ: 56.14, 60.77, 60.91, 70.42, 86.68, 101.77, 107.97, 109.54, 109.58, 123.80, 125.53, 133.98, 141.99, 147.68, 151.71, 153.30, 153.63, 165.43. FAB-MS (positive ion mode) m/z : 472 $[M]^+$. *Anal.* Calcd for $C_{18}H_{17}O_7I$: C, 45.78; H, 3.63. Found: C, 45.50; H, 3.56.

2,2'-Bis(6-iodo-1,3-benzodioxol-5-ylmethyl 3,4,5-trimethoxybenzoate) (**12**)

Colorless prisms mp 131—133℃ (CH_2Cl_2-Et_2O-hexane). IR ($CHCl_3$) cm^{-1} : 3020, 1710, 1480, 1325, 1220, 1205, 1100, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.55 (6H, s), 3.85 (6H, s), 3.92 (6H, s), 4.99 (2H, d, *J* = 13.0), 5.00 (2H, d, *J* = 13.0), 5.97 (4H, s), 6.57 (2H, s), 7.18 (2H, s), 7.38 (2H, s). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: .55.71, 60.49, 60.61, 70.55, 87.06, 101.72, 109.27, 110.01, 118.31, 124.51, 126.39, 131.37, 145.43, 148.16, 148.19, 150.88, 151.86, 166.19. *Anal.* Calcd for $C_{36}H_{32}O_{14}I_2$: C, 45.88; H, 3.42. Found: C, 46.08; H, 3.62.

6-Iodo-1,3-benzodioxol-5-ylmethyl 3,4,5-trimethoxybenzoate (**13**)

Colorless needles mp 152—153.5℃ (CH_2Cl_2-Et_2O). IR (KBr) cm^{-1} : 2940, 1720, 1590, 1505, 1480, 1460, 1420, 1340, 1230, 1135. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.91 (12H, s), 5.29 (2H, s), 5.99 (2H, s), 6.98 (1H, s), 7.30 (1H, s), 7.35 (2H, s). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 56.21, 60.85, 70.35, 87.14, 101.82, 106.95, 110.25, 118.85, 124.81, 131.74, 142.31, 148.37, 148.47, 152.88, 165.74. *Anal.*Calcd for $C_{18}H_{17}O_7I$: C, 45.78; H, 3.63. Found: C, 45.93; H, 3.91.

1,2,3-Trimethoxy-9,10-methylenedioxy-7*H*-dibenzo[c,e]oxepin-5-one (**14**)

Colerless needles mp 162—166℃ (CH_2Cl_2-Et_2O). IR (KBr) cm^{-1} : 2950, 1710, 1600, 1510, 1490, 1410, 1330, 1250, 1110, 1040, 930, 890. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.65 (3H, s), 3.95 (3H, s), 3.99 (3H, s), 4.80 (1H, d, *J* = 12.0), 4.94 (1H, d, *J* = 12.0), 6.02 (1H, d, *J* = 1.4), 6.07 (1H, d, *J* = 1.4), 6.92 (1H, s), 7.21 (1H, s), 7.26 (1H, s). FAB-MS (positive ion mode) m/z : 344 $[M]^+$. HRMS (FAB) Calcd for $C_{18}H_{16}O_7$ $[M]^+$: 344.0896. Found : 344.0858.

Reduction of 9

To a solution of **9** (100 mg, 0.106 mmol) in toluene (2 mL) DIBAL (1.0 M toluene solution, 0.530 mL, 0.530 mmol) was added dropwise, and the mixture was then stirred for 1 h at -78°C. A sodium hydroxide aqueous solution (1N, 10 mL) was added and the mixture was stirred for 30 min at rt. After extraction with ether, the organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a residue which was subjected to silica gel column chromatography with ether - chloroform (1:20). Alcohol (**7**, 46.0 mg, 67%) was obtained from the less polar fraction and **15** (21.9 mg, 68%) from the more polar fraction, and the starting material (**9**, 32.3 mg, 32%) was also recovered.

6,6'-Bis(5-hydroxymethyl-1,3-benzodioxole) (**15**) [16]

Colorless needles mp 182—182.5℃ ($CHCl_3$). IR (KBr) cm^{-1} : 3300, 2900, 1500, 1480, 1245, 1065, 1040, 930, 860. ^{1}H-NMR (200 MHZ, $CDCl_3$-acetone) δ: 2.89 (2H, s, exchange with D_2O), 4.22 (4H, s), 6.01 (4H, s), 6.58 (2H, s), 7.01 (2H, s). *Anal.* Calcd for $C_{16}H_{14}O_6 \cdot 0.5H_2O$: C, 61.73; H, 4.86. Found: C, 61.75; H, 4.69.

Reduction of 12

To a solution of **12** (200 mg, 0.212 mmol) in toluene (3 mL) DIBAL (1.0 M toluene solution, 2.12 mL, 2.12 mmol) was added dropwise, and the mixture was then stirred for 30 min at -78°C. A sodium hydroxide aqueous solution (1N, 20 mL) was added and the mixture was stirred for 30 min at rt. After extraction with ether, the organic layer was washed with brine, dried over magnesium sulfate, and evaporated to give a residue which was subjected to silica gel column chromatography with ethyl acetate

- hexane (2:1). Alcohol (**8**, 111 mg, 94%) was obtained from the less polar fraction and **16** (62 mg, 74%) from the more polar fraction.

2,2'-Bis[1-(hydroxymethyl)-3,4,5-trimethoxybenzene] (16)[17]

Colorless prisms mp 96.5－97.5℃ (Et_2O-hexane) [lit.,[17]106－108℃ (*R*-**16**) (Et_2O-hexane)]. IR (KBr) cm^{-1} : 3400, 2950, 1600, 1490, 1460, 1400, 1325, 1195, 1130, 1105, 1010, 980. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.67 (6H, s), 3.89 (6H, s), 3.93 (6H, s), 4.18 (4H, s), 6.89 (2H, s). FAB-MS (positive ion mode) m/z : 394 $[M]^+$. *Anal.* Calad for $C_{20}H_{26}O_8$: C, 60.90; H, 6.64. Found: C, 60.56; H, 6.86.

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