MONOACETOXYLATION OF METHYLENEDIOXY GROUPS IN DIMETHYL 4,4'-DIMETHOXY-2,3,2'3'-BISMETHYLENEDIOXY-1,1'-BIPHENYL-6,6'-DICARBOXYLATE WITH LEAD TETRAACETATE

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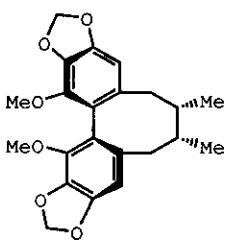
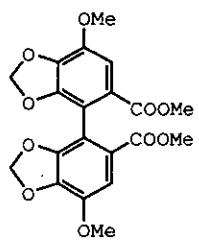
Abstract — The utility of lead tetraacetate as a reagent for the monoacetoxylation of a methylenedioxy group in dimethyl 4,4'-dimethoxy-2,3,2'3'-bismethylenedioxy-1,1'-biphenyl-6,6'-dicarboxylate (**1a**) is demonstrated. Mechanistic feature of the monoacetoxylation is discussed.

The antihepatotoxic effect of the lignans which contain methylenedioxy groups in the molecule and isolated from the fruits of Schizandra Chinensis has previously been reported by chinese group.[1]

During the investigation of the finding new synthetic drugs for a hepatopathy, the chinese group found that **1a** (BDD) was effective in protecting the liver from CCl_4 injury.[2,3] BDD which was prepared from gallic acid as a intermediate of schizandrin C analog synthesis, has been used for the improvement of symptoms in chronic hepatitis in China.

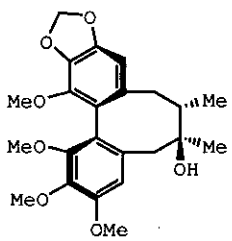


Schizandrin C

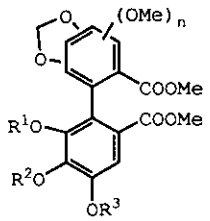


1a (BDD)

The chinese group[1] and our group[4] found that gomisin A having a methylenedioxy group in one of the aromatic rings exhibited the strongest activity among various schizandrin C analogs. These results suggested that the unsymmetrical biaryl having a methylenedioxy group possesses the stronger activity than the symmetrical one. So, the synthesis of unsymmetrical biaryl (I) corresponding to gomisin A was planned.



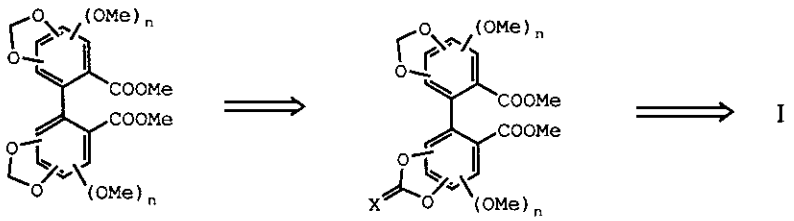
Gomisin A



I

Several unsymmetrical biaryl syntheses by the cross[5] or intramolecular[6] coupling of two aromatic parts have recently been reported in the literatures. Unfortunately, these methods in the synthesis of highly functionalized biaryl derivatives may be impractical for large scale production due to troublesome preparation of the each aromatic part or the length of the synthetical process.

In our search for a practical approach to unsymmetrical biaryl (I), the simple route *via* the conversion of readily available symmetrical biaryl (II) into unsymmetrical one (III) by the selective oxidation of one of methylenedioxy groups prior to the cleavage of it was considered.



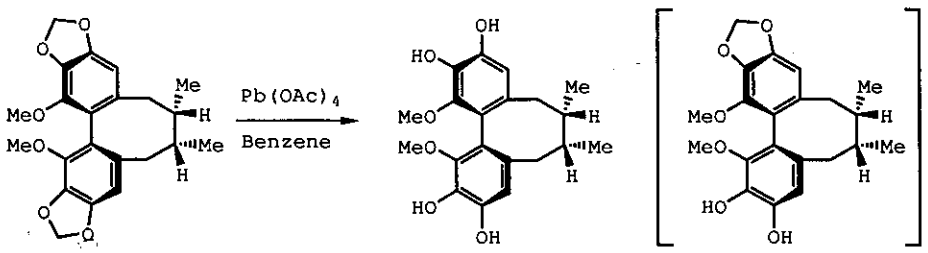
II III

Scheme 1 X=O; halogens; OAc, H

In this paper we wish to report the monoacetoxylation of a methylenedioxy group in symmetrical biaryl (**1a**) (R=H, BDD) for the conversion to unsymmetrical one (**3a**).

The selective cleavage of a methylenedioxy group in compound (II) using PCl_5 or BCl_3 was unsuccessful even if the reagent was used stoichiometrically. Ikeya group[7a] and Yamaguchi group[7b] reported a cleavage of the methylenedioxy group with lead tetraacetate [$Pb(OAc)_4$] oxidation in benzene, followed by treating with 80% acetic acid during the course of studies on the lignans. Ikeya group also reported that in the oxidation of schizandrin C (wuweizisu C) with $Pb(OAc)_4$ (3.5 eq.) non of monocatechol (V) but biscatechol (IV) was obtained by randam attack of $Pb(OAc)_4$ to methylenedioxy groups in it.[8]

No study has been reported on the chelation of $Pb(OAc)_4$ with carbonyl group. However, it has been

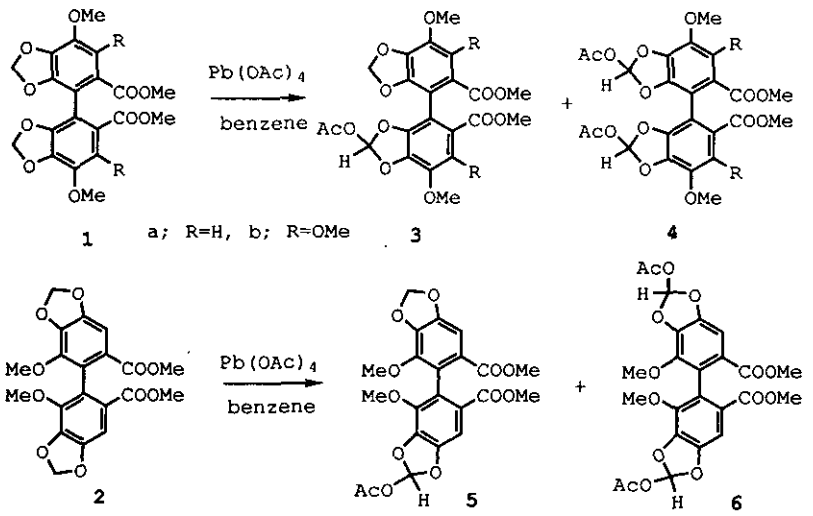


Schizandrin C IV (32%) V

Scheme 2

reported that in the complex of Pb(II) with pyridine-2,6-dicarboxylic acid the lead atom was six coordinate with approximately pentagonal pyramidal geometry.[9] In the case of symmetrical biaryl (II) having ester groups it was presumed that the methoxycarbonyl groups would first make a rigid complex with $Pb(OAc)_4$ by formation of the chelation. After the oxidation of a methylenedioxy group, the other one would be hindered from the second attack of $Pb(OAc)_4$ by an acetoxyl group introduced. Accordingly it was expected that one of methylenedioxy groups in biaryl (II) could be oxidized selectively.

In practice, we have found that one of methylenedioxy groups in biaryl (**1a**) was selectively oxidized with 3 equivalents of $Pb(OAc)_4$ to afford compound (**3a**) (Scheme 3, Table 1). **3a** was obtained as a mixture containing the starting material (**1a**) after the reaction. As the separation of **3a** and **1a** was unsuccessful because of the anomalous reactivity of **3a** with silica gel, this material was used directly in subsequent reaction. The presence of the diastereomers in compound (**3**) was suggested by the observation of two singlets (2.06 and 2.09 ppm) for three protons of acetyl group in ^{1}H-nmr. However, the conformational analyses of each isomer were not determined because of the unsuccessful purification of them. While the oxidation of biaryl (**1b**)[10] or (**2**)[2] with $Pb(OAc)_4$(1.5 eq.) afforded the mixture of mono- and diacetoxyl derivatives (**3b** and **4b**), or (**5** and **6**), respectively (Scheme 3 and Table 1). Even though less than 1 equivalent of $Pb(OAc)_4$ was used for the oxidation of **1b** and **2**, diacetoxyl derivatives (**4b**) and (**6**) were formed as the by-products in spite of remaining of the starting material, respectively.



Scheme 3

Table 1

entry	starting material	$Pb(OAc)_4$(eq.)	products (ratio*)
1	**1a**	3.0	**3a** : **4a** 100 : 0
2	**1b**	1.5	**3b** : **4b** 68 : 32
3	**2**	1.5	**5** : **6** 67 : 33

* The ratios were determined by ^{1}H-nmr.

Compound (**3**) was then led to compound (**7a**) in two steps (i ; 80% AcOH, ii; Me_2SO_4/K_2CO_3/MeOH) which was identified by the elemental analysis. Compounds (**3b, 4b, 5**, and **6**) were also led to **7b, 8, 9**, and **10** in the same manner described above, respectively. Compounds (**7a-10**) were identified by the elemental analyses and high resolution mass spectra.

The retios of **7b : 8** or **9 : 10** were in rough accord with the ratios of **3b : 4b** or **5 : 6** by ^{1}H-nmr spectra, respectively.

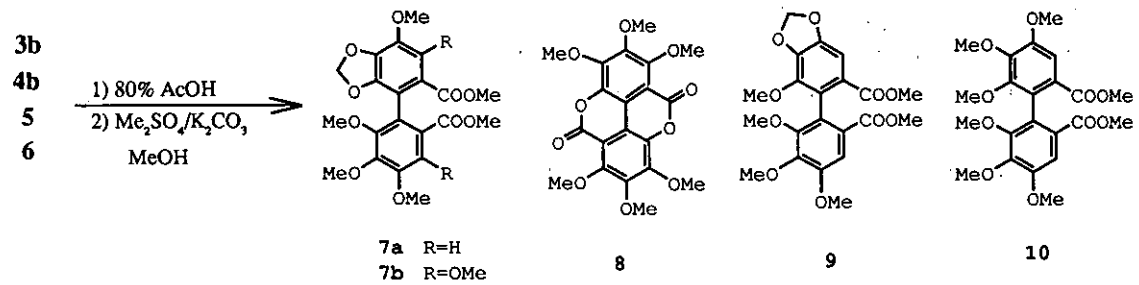


Table 2

staring material	acetoxyl intermediate	product	overall yield from starting material (%)	
1a	**3a**	**7a**	65	
1b	**3b**	**7b**	32	
1b	**4b**	**8**	16	(**7b/8** = 67/33)
2	**5**	**9**	41	(**9/10** = 63/37)
2	**6**	**10**	25	

A plausible mechanism for the monoacetoxylation of **1a** is depicted in Figure 1.

This selectivity was rationalized by the existence of the chelated intermediate which was derived by the coordination of $Pb(OAc)_4$ with the carbonyl groups of methyl esters.

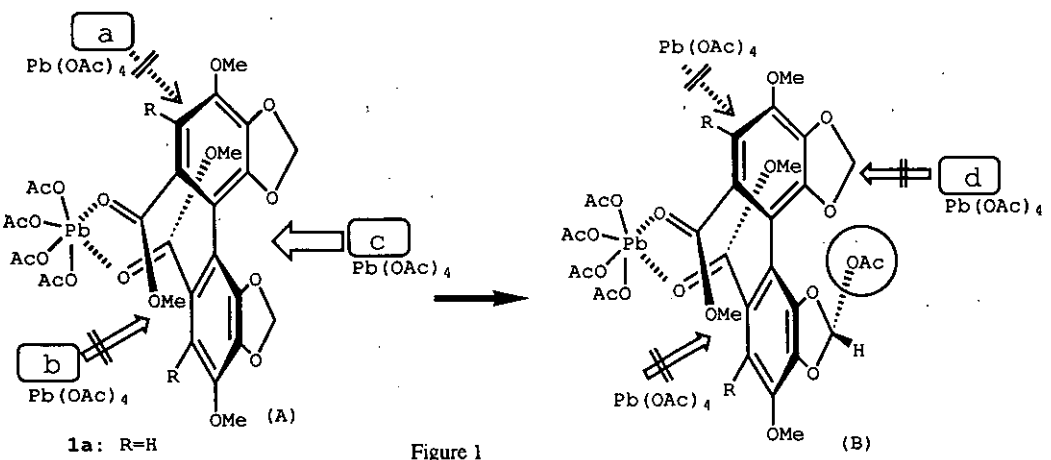


Figure 1

First, one mole of $Pb(OAc)_4$ is utilized in the coordination with biaryl (**1a**) to make a rigid chelated ring. Then two sides (a and b) are shielded by two methoxy groups of the ester moieties, and second, the rest of $Pb(OAc)_4$ attacks from the less hindered side (c) and oxidizes a methylenedioxy group to yield acetoxyl derivative (B) .

As shown in Figure 1, excess of $Pb(OAc)_4$ can no longer attack to the other methylenedioxy group of intermediate (B) from the side (d) because of the steric hindrance by the introduced acetoxyl group.

The presence of substituents (R=OMe) at C 5,5' in compound (**1b**) might retard formation of the chelated intermediate, and the selectivity becomes lower than compound (**1a**) (entry 2 in Table 1). Biaryl (**2**) may also be able to make the chelation with $Pb(OAc)_4$, both methylenedioxy moieties are however not shielded by any functional groups in it, and may be randomly attacked by $Pb(OAc)_4$.

Experimental

Melting points were determined on a YANACO MP-J3 and are uncorrected. ^{1}H-Nmr spectra were obtained with a JEOL FX-200 and a Varian FT-80A using $CDCl_3$ as a solvent. Ir spectra were recorded on a HITACHI 270-30 spectrophotometer. High resolution mass spectra and mass spectra were obtained on a JEOL DX-300 and a KRATOS CONCEPT 1H mass spectrometer. Elemental analyses were performed on a Heraeus CHIN-)-PAPID Elemental Analyzer.

General procedure for the acetoxydation of biaryls (**1a**, **1b**, and **2**)

Synthesis of acetoxyl derivative (**3a**)

To a benzene (50 ml) solution of biaryl (**1a**) (4.18 g, 10 mmol) was added lead tetraacetate (13.3 g, 30 mmol). The mixture was refluxed for 5 h and treated with ethylene glycol (10 ml). Lead diacetate was filtered off through a celite. The filtrate was then washed with water, dried over anhydrous sodium sulfate and evaporated to give a mixture of **3a** and **1a** (4.15 g). As the separation of **3a** and **1a** was unsuccessful because of the anomalous reactivity of **3a** with silica gel, this material was used directly in subsequent reaction.

3a ^{1}H-Nmr (80 Mz, $CDCl_3$) δ: 7.70(1H, s, >CH-), 5.97(2H, s, $-CH_2-$), 2.06 and 2.09(3H, s, $-CH_3$)

Syntheses of acetoxyl derivatives (**3b**, **4b**, **5**, and **6**)

In the similar manner as a bove, except for the use of the equivalent of $Pb(OAc)_4$ (1.5 eq.), **1b** or **2** yielded a mixture of acetoxyl derivatives (**3b** and **4b**) or (**5** and **6**), respectively.

3b ^{1}H-Nmr (200 Mz, $CDCl_3$) δ: 7.66 (0.5H, s, >CH-), 7.65 (0.5H, s, >CH-), 5.93-5.97 (2H, m, $-CH_2-$), 2.12 (0.5H, s, $-CH_3$), 2.11 (1.5H, s, $-CH_3$).

4b ^{1}H-Nmr (200 Mz, $CDCl_3$) δ: 7.67 (2H, s, >CH-), 2.15 (6H, s, $-CH_3$).

5 ^{1}H-Nmr (200 Mz, $CDCl_3$) δ: 7.77 (1H, s, >CH-), 6.06 (2H, s, $-CH_2-$), 2.16 (3H, s, $-CH_3$).

6 ^{1}H-Nmr (200 Mz, $CDCl_3$) δ: 7.77 (2H,s, >CH-), 2.16 (6H, s, $-CH_3$).

General procedure for the preparation of compounds (**7a** - **10**)

Synthesis of compound (**7a**)

A solution of crude compound (**3a**) (4.15 g) in 80 % acetic acid (50 ml) was refluxed for 5 h. After

evaporation of acetic acid in vacuo, the residue was treated with dimethyl sulfate (6.3 g, 50 mmol) and potasium carbonate (6.9 g, 50 mmol) in methanol (200 ml). After refluxing overnight, the solvent was removed. The residue was dissolved in ethyl acetate (100 ml), washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Compound (**7a**) (2.82 g, 65 % from **1a**) and starting material (**1a**) (631 mg) were separated from the residue by column chromatography on silica gel.

7a Yield 65 % from **1a**. Colorless crystals, mp 94-95°C (benzene). Ir (KBr) ν : 1722. ^{1}H–Nmr (200 Mz, $CDCl_3$) δ: 7.39 (1H, s), 7.37 (1H, s), 5.96 (2H, s), 3.97 (3H, s), 3.94 (3H, s), 3.93 (3H, s), 3.65 (3H, s), 3.61 (6H, s). Ms m/z 434 (M^+). Anal. Calcd for $C_{21}H_{22}O_{10}$: C, 58.06 ; H, 5.11. Found: C, 58.04; H, 5.04.

Syntheses of compounds (**7b, 8, 9,** and **10**) were similarly prepared.

Compounds (**7b** and **8**)

7b Yield 65 % from **1b**. Ir (KBr) ν : 1730. ^{1}H-Nmr (80 Mz, $CDCl_3$) δ: 5.92 (2H, s), 4.05 (3H, s), 3.96 (3H, s), 3.95 (3H, s), 3.87 (3H, s), 3.85 (3H, s), 3.70 (3H, s), 3.64 (3H, s), 3.59 (3H, s). Hrms : m/z 494 (M^+), Calcd for $C_{23}H_{26}O_{12}$: 494.14243. Found: 494.14257.

8 Yield 44 % from **1b**. Ir (KBr)ν : 1744. ^{1}H-Nmr (200 Mz, $CDCl_3$) δ: 4.26 (6H, s), 4.03 (6H, s), 4.02 (6H, s). Ms (FAB) m/z 419 (M+1). Anal. Calcd for $C_{20}H_{18}O_{10}$: C, 57.42; H,4.34. Found: C, 57.36; H, 4.28.
1b was recovered in 13 % yield.

Compounds (**9** and **10**)

9 Yield 41 % from **2**. Ir (KBr) ν : 1726. ^{1}H-Nmr (80 Mz, $CDCl_3$) δ: 7.37 (1H, s), 7.25 (1H, s), 6.06 (2H, s), 3.94 (6H, s), 3.78 (3H, s), 3.65 (3H, s), 3.61 (3H, s), 3.59 (3H, s). Ms m/z 434 (M^+). Anal. Calcd for $C_{21}H_{22}O_{10}$: C, 58.06; H, 5.11. Found: C, 57.95; H, 5.21.

10 Yield 25 % from **2**. Colorless crystals, mp 94.5-96°C (benzene). Ir (KBr)ν : 1728. ^{1}H-Nmr (80 Mz, $CDCl_3$) δ: 7.36 (2H, s), 3.95 (6H, s), 3.94 (6H, s), 3.60 (12H, s). Ms m/z 450(M^+). Anal. Calcd for $C_{22}H_{26}O_{10}$: C, 58.66; H, 5.82. Found: C, 58.63; H, 5.82.
2 was recovered in 10 % yield.

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