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Synthesis of New Schizandrin Analogues

Jun Biao CHANG[1]*, Jing Xi XIE[2]

[1]Henan Institute of Chemistry, Henan Academy of Sciences, Zhengzhou 450002
[2]Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050

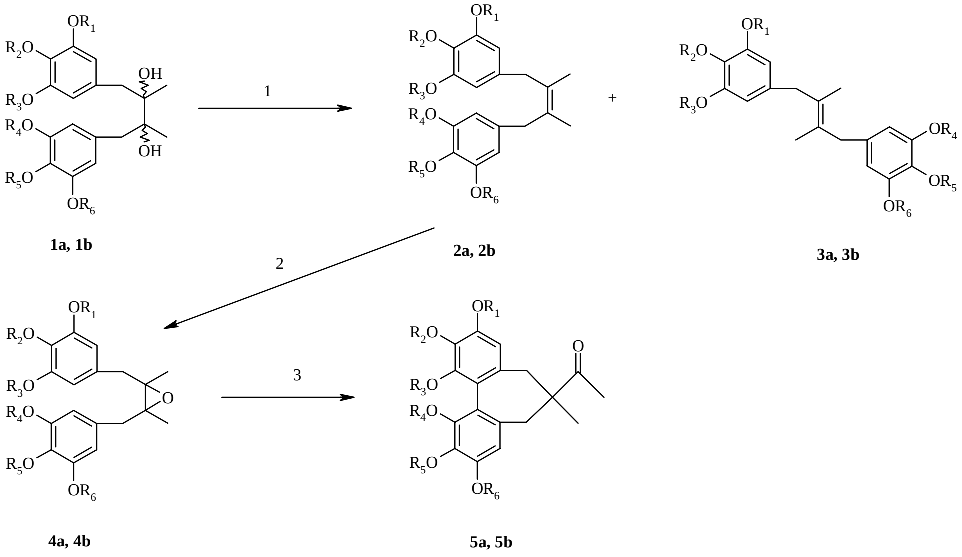
Abstract: Two new lignans with dibenzocycloheptadiene skelectons have been synthesized by intramolecular nonphenolic oxidative coupling and rearrangement. The structures of these products have been identified by MS, UV, IR and NMR spectra.

Keywords: Schizandrin analogues, intramolecular nonphenolic oxidative coupling, DDQ.

The lignans are groups of natural products, most of these compounds have various biological activities[1]. Such as schisandrin possesses extensive significant anti-convulsive activities, particularly regarding cerebral protection and adjustment of the cerebral cortex′s excitement inhibition process. Therefore, it is of interest to synthesize schzandrin and its analogues as potential CNS inhibitory agents.

As a part of our drug discovery program for CNS inhibitory agents, we wanted to synthesize analogs of schizandrin, which require a key intermediate such as compound **4** (**Scheme 1**). Due to our previous successful experience[2], the hydroxy groups in compound **1a**, **1b** should be protected because they interfered an intramolecular aryl-aryl oxidative coupling reaction. Therefore, we designed and synthesized an epoxide intermediate **4a**, **4b** in order to synthesize analogs of schizandrin by the oxidative coupling reaction with 2, 3-dichloro-5, 6-dicyano-1, 4-benzo-quinone (DDQ) in trifluoroacetic acid (TFA). Treatment of compound **1a**, which is a mixture of erythro and threo isomers, with ethyl orthoformate in the presence of benzoic acid at 180°C afforded the corresponding (*Z*)-and (*E*)-butenes (**2a** and **3a**) in 90% yield, with a ratio of 1:1, which could be separated easily by simple recrystallization from EtOH. Then, epoxidation of **2a** with 3-chloroperoxy-benzoic acid in CH_2Cl_2 and KH_2PO_4/Na_2HPO_4 (0.5 g, 3.7 mmol/0.5g, 3.5 mmol) buffer solution afforded 1, 4-diaryl-2, 3-epoxy-2, 3-dimethylbutane **4a**[3]. DDQ is a kind of oxidative reagent. The biaryl lignans are converted by the reaction of DDQ with 1, 4-diarylbutane, DDQ is the first nonphenolic oxidative coupling regent ever reported without any transition metal. As part of our ongoing DDQ developments, the nonphenolic oxidative coupling reaction and mechanism of 1,4-diarylbutane with DDQ in TFA were reported. To a mixture of 1, 4-diaryl-2, 3-dimethyl-2, 3-epoxide **4a** (1.0 g, 0.18mol) and DDQ (0.9 g, 4 mmol) was added fresh distilled TFA (15ml) and the mixture was stirred for 3.5 h at room temperature. TLC showed that the starting material disapptared. The reaction mixture was poured into ice water and extracted with benzene. The benzene extract was washed successively with aq. $NaHCO_3$, aq. NaOH and brine. After removal of the solvent, instead of the expected dibenzocyclooctadiene, a new compound **5a**[4] with a dibenzocycloheptadiene skeleton was obtained yielding 45.2% by rearrangement and cyclization (**Scheme 2**).

Scheme 1



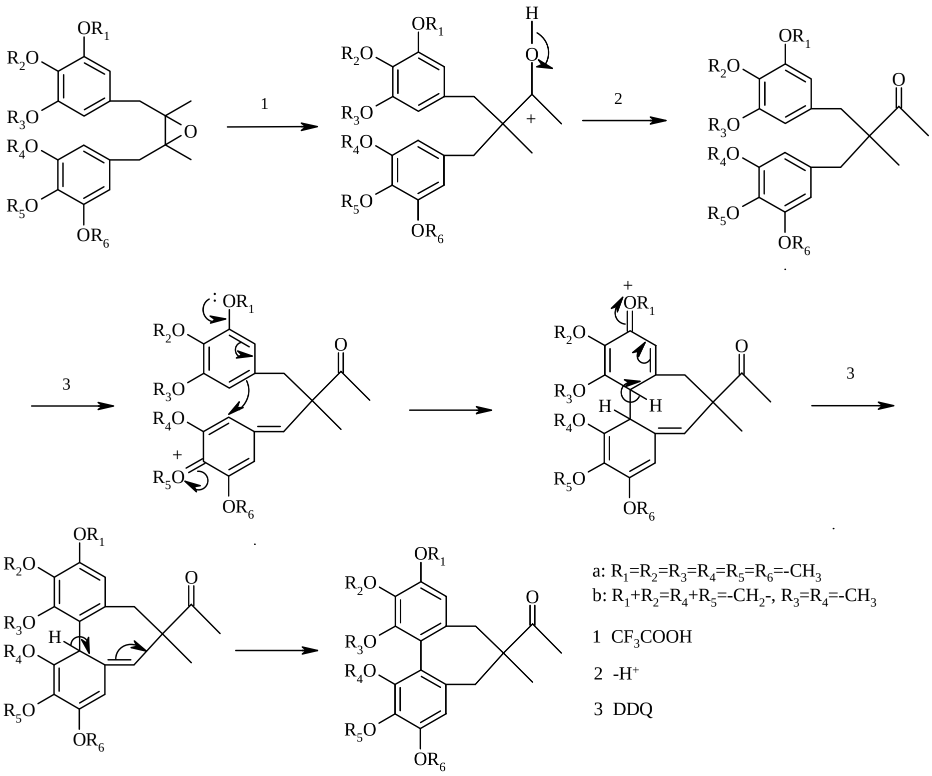
a: $R_1=R_2=R_3=R_4=R_5=R_6=CH_3$
b: $R_1+R_2=R_5+R_6=CH_2$; $R_3=R_4=CH_3$

1 ethyl orthoformate
2 MCPBA
3 DDQ/TFA

Compound **5a**, MS spectrum [M+430(100)], ^{1}HNMR spectrum (shown two aromatic hydrogen signals at 6.54 and 6.56 ppm) and UV spectrum (262 and 218 nm) showed the characteristic peaks of a biphenyl compound, ^{13}CNMR (211.56 ppm) and IR spectra (1710 cm^{-1}) gave the evidence for a carbonyl group. Accordingly, we identified **5a** as 1, 2, 3, 11, 12, 13-hexamethoxy-7-methyl-7-acetyl dibenzocycloheptadiene. **4b**, **5b**[5] were synthesized from **1b** by the same procedures as **5a**. The aryl-aryl coupling position of **5b** may possess the one of the following structures (**Scheme 3**).

From **Scheme 3**, methyl group of acetyl is very closely to the aromatic hydrogen in the form I and II. But in the form III, it is rather far from aromatic hydrogen. So the intensity of the aromatic hydrogen in ^{1}HNMR spectrum should be increased clearly when acetyl group was irradiated for the structure I or II. In the structure III, the aromatic hydrogen should be increased when methoxyl groups were irradiated.

Scheme 2



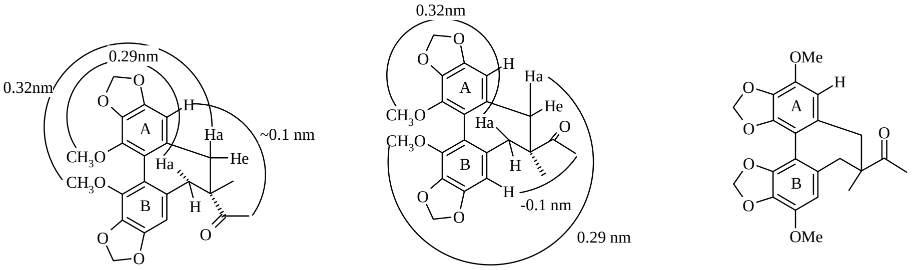
a: $R_1=R_2=R_3=R_4=R_5=R_6=\text{-}CH_3$
b: $R_1+R_2=R_4+R_5=\text{-}CH_2\text{-}$, $R_3=R_4=\text{-}CH_3$

1 CF_3COOH

2 $\text{-}H^+$

3 DDQ

Scheme 3



I II III

The NOE experiment of compound **5b** showed that the aromatic hydrogen increased 0% when methoxyl groups were irradiated. While the aromatic hydrogen increased 30% when acetyl group was irradiated. These results suggested that the compound **5b** existed in the form I or II.

The biological evaluations of the compound **5a** and **5b** are in progress in our laboratories.

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References and Notes

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3. Compound **4a**: white crystals; mp 93-94°C; ^{1}HNMR ($CDCl_3$, δ ppm) 1.32 (s, 6H, $2\times CH_3$); 1.62-2.97 (q, 4H, $2\times CH_2$), 3.86 (s, 18H, $6\times OCH_3$); 6.49 (s, 4H, 4×ArH); Anal. Calcd for $C_{24}H_{32}O_7$: C 66.65, H 7.46, Found: C 66.67, H 7.45.
4. Compound **5a**: White crystals; mp 112-113℃; ^{1}HNMR ($CDCl_3$, δ ppm) 1.16 (s, 3H, CH_3), 2.18 (s, 3H, $COCH_3$), 1.89-3.03 (q, 4H, $2\times CH_2$), 3.68 (s, 6H, $2\times OCH_3$), 3.88 (s, 6H, $2\times OCH_3$), 3.92 (s, 6H, $2\times OCH_3$), 6.54 (s, 2H, 2×ArH); Anal. Calcd for $C_{24}H_{30}O_7$: C 66.96, H 7.02; Found: C 66.90, H 6.99.
5. Compound **4b**: White crystals; mp 96-97°C, ^{1}HNMR ($CDCl_3$, δ ppm) 1.76 (s, 6H, $2\times CH_3$), 3.40 (s, 4H, $2\times CH_2$), 3.89 (s, 6H, $2\times OCH_3$), 5.94 (s, 4H, $2\times OCH_2O$), 6.36 (d, 4H, J=1.5Hz, 4×ArH); Anal. Calcd for $C_{22}H_{24}O_7$: C, 65.99, H, 6.04, Found: C, 65.70, H, 6.01.
   Compound **5b**: White crystals; mp 127-128℃ ^{1}HNMR ($CDCl_3$, δ ppm) 1.11 (s, 3H, CH_3), 1.93-2.84 (q, 4H, $2\times CH_2$), 2.15 (s, 3H, $COCH_3$), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.92 (d, 2H, J=1.0, OCH_2O), 5.96 (d, 2H, J=1.0, OCH_2O), 6.44 (s, 1H, ArH), 6.47(s, 1H, ArH) Anal. Calcd for $C_{22}H_{22}O_7 \cdot 0.5H_2O$: C, 64.91, H, 5.67, Found: C, 64.89, H, 5.66

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