

Asymmetric Synthesis of (S)-Dimethyl -4, 4'-dimethoxy-5, 6, 5', 6'-dimethenedioxybiphenyl-2, 2'-dicarboxylate

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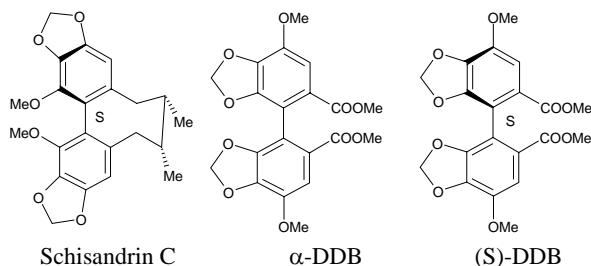
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Abstract: (S)-Dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethenedioxy-biphenyl-2, 2'-dicarboxylate was synthesized in reasonable yield through a series of reactions, including chiral oxazoline-mediated asymmetric Ullmann coupling, from methyl 2-bromo-5-methoxy-3, 4-methenedioxybenzoate.

Keywords: Biphenyl, Schisandrin C, asymmetric Ullmann coupling.

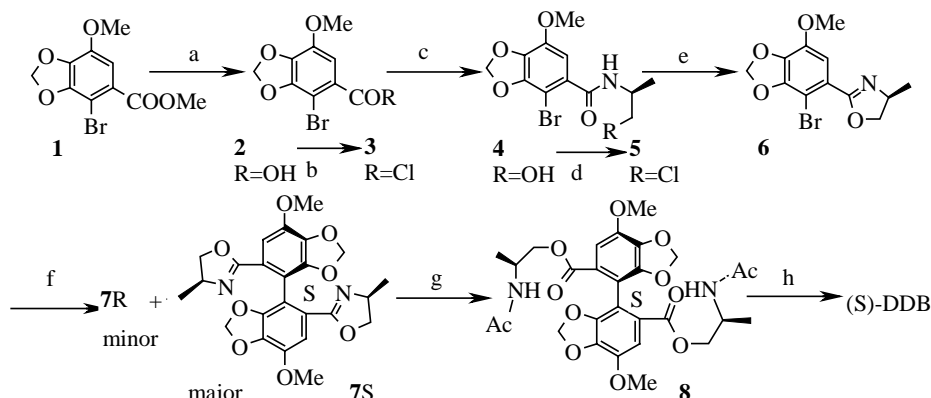
Schizandra chinensis (wuweizi) has long been used in Chinese herbal medicine. Schisandrin C, as a constituent of *Schizandra chinensis*, shows various pharmacological activities¹. The similar compound, dimethyl-4, 4'-dimethoxy-5, 6, 5', 6'-dimethenedioxy-biphenyl-2, 2'-dicarboxylate (α -DDB), discovered by Xie^{2,3} *et al.* in the investigation of schisandrin C, and some derivatives have also exhibited anti-HIV and anti-HBV activity⁴. Further study of this kind of biphenyls has attracted considerable attention.

It is well known that 2, 2', 6, 6'-tetra-substituents of biaryl make it difficult to rotate about aryl-aryl bond, which could result in two axially chiral isomers with R/S configuration. Furthermore, R and S isomers showed different biological activities⁵. To date, there is scarce report on the preparation of chiral α -DDB besides classical resolution of α -DDB's racemic isomers⁶. Therefore, it is necessary to find an efficient stereoselective method of synthesizing DDB. This paper described that S-DDB was prepared in reasonable yield.



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Scheme 1



Reagent: (a) 1. KOH, in 95% EtOH; 2. Conc. HCl; (b) SOCl₂, in CH₂Cl₂; (c) (S)-2-aminopropanol, Et₃N in CH₂Cl₂; (d) SOCl₂, Et₃N; (e) *t*-ButOK, THF and *t*-ButOH; (f) activated copper dust in DMF; (g) 1. TFA, water. 2. Ac₂O, DMAP; (h) NaOMe, in MeOH.

(S)-DDB was synthesized as **Scheme 1** from methyl 2-bromo-5-methoxy-3,4-methenedioxybenzoate **1** *via* a series of reactions including the key chiral oxazoline-mediated asymmetric Ullmann coupling reaction⁷.

1 was hydrolyzed to afford **2**, and then **2** was converted to the carboxylic chloride **3** by the reaction with SOCl₂. **3** was mixed with (S)-2-aminopropanol and triethylamine to afford **4**. Reaction of the amide **4** with SOCl₂ gave **5**, and **5** was heated in the presence of potassium *t*-butoxide in the mixed solvent of THF and *t*-butanol to give (S)-oxazoline phenyl bromide **6**.

The asymmetric Ullmann coupling reaction of **6** in the presence of activated copper powder gave the mixture of bis-oxazoline biphenyl **7S** and **7R**. HPLC and ¹³C NMR analysis indicated that the diastereomeric ratio of S and R was 81:19. Recrystallization in the mixture of CH₂Cl₂ and light petroleum afforded the optical pure **7S**.

S-Configuration of the biphenyl subunit of **7S** was confirmed by Cotton effect in CD spectrum. The CD spectroscopy of **7S** exhibited negative Cotton effect at 305 nm, 260 nm and positive Cotton effect at 293 nm in methanol. Therefore, the configuration of compound **7S** was assigned as S⁸. In addition, the configuration was also confirmed by the specific rotation of the related compound S-DDB.

As a pair of diastereoisomers, **7R** and **7S** could be separated on HPLC by general C18 column. The retention time of **7S** and **7R** were 25.7 min and 27.6 min, respectively, at given condition. In addition, ¹³CNMR spectrum of **7S** showed twelve single-peaks, but the mixture of **7S** with minor **7R** exhibited twelve pairs of double-peaks. The peak intensity ratio of double-peaks was approximately consistent with the ratio of S and R measured by HPLC.

7S was hydrolyzed and reacted with acetic anhydride to give diamide **8**, and the crude of **8** was alcoholysized by methanol in the presence of sodium methoxide to afford S-DDB. The CD spectroscopy showed negative Cotton effect at 259 nm. Therefore, the configuration of **8** was assigned as S⁹.

Experimental

¹H NMR spectra were recorded on a Bruker-300 MHz. IR spectra, ESI-MS and circular dichroism spectroscopy were carried out on a Shimadzu IR-408, Bruker Esquire-3000 and Jasco J-20, respectively. HPLC were on Shimadzu LC-10A.

Compound 4: Methyl 2-bromo-5-methoxy-3,4-methenedioxybenzoate **1** (6 g, 20.7 mmol) was added to water (60 mL) with KOH (4.5 g, 69 mmol). The mixture was refluxed for 7 h, and then acidified with con.HCl till pH=3.0. Filtration and dryness of the mixture gave corresponding benzoic acid **2** (5.48 g, 96%). CH₂Cl₂ (100 mL), SOCl₂ (2.8 mL, 39 mmol) and 2 drops DMF were added to compound **2** (5.20 g, 18.9 mmol). After the mixture was stirred for 12 h, the solution was evaporated under reduced pressure. Toluene (10 mL) was added to the residue. The solvent was evaporated again to afford crude **3**. The solution of **3** in CH₂Cl₂ (30 mL) was added to the mixture of CH₂Cl₂ (30 mL), (S)-2-amino propanol (1.56 g, 20.8 mmol) and triethyl- amine (5 mL) at cooling in ice bath. This mixture was stirred for 12 h at r.t. under Ar, and poured into 100 mL water. The organic layer was separated and dried over Na₂SO₄, and evaporated in *vacuo*. Recrystallization from ethanol gave **4** (5.27 g) in 84% yield. mp. 175-176 °C. ¹H NMR (300 MHz, CDCl₃, δ ppm) 6.97(s, 1H, Ar-H), 6.10(s, 2H, OCH₂O), 4.28(m, 1H, NCH), 3.92(s, 3H, OCH₃), 3.83-3.78(dd, 1H, J=3.3, 10.8 Hz, OCH), 3.69-3.64(dd, 1H, J=5.4, 10.8 Hz, OCH), 1.31(d, 3H, J=6.9, CH₃). IR(KBr, cm⁻¹) 3278.8 (O-H), 1643.2, 1624.0 (CONH). ESI-MS(*m/z*) 332 [M+H]⁺.

Compound 6: SOCl₂ (2.40 mL, 33 mmol) was added to the solution of **4** (5 g, 15 mmol) in CH₂Cl₂ (100 mL). The mixture was stirred at r.t. overnight and poured into 120 mL ice water. The aqueous 10% NaOH was added till pH 7. The organic layer was separated and dried over Na₂SO₄, and the solvent was removed in *vacuo* to give **5**. To **5** were added THF (75 mL), potassium *t*-butoxide (3.36 g, 30 mmol) in *t*-butanol (75 mL). The mixture was stirred at reflux overnight. The solvent was removed, 30 mL water was added and then was extracted with CH₂Cl₂ (3×50 mL). The CH₂Cl₂ extract was dried over Na₂SO₄ and evaporated. The residue was purified by silica gel chromatography to yield (S)-oxazoline phenyl bromide **6** in 95% yield (4.5 g). mp. 83-84 °C, [α]_D²⁵ = -36.1 (c 3.1, CHCl₃), ¹H NMR (300 MHz, CDCl₃, δ ppm) 7.06(s, 1H, Ar-H), 6.10(s, 2H, OCH₂O), 4.54-4.48(dd, 1H, J=7.8, 9 Hz, OCH^a), 4.43-4.38(m, 1H, NCH), 3.97(t, 1H, J=7.5 Hz, OCH^b), 3.91(s, 3H, OCH₃), 1.38(d, 3H, J=6.3 Hz, CH₃). ESI-MS(*m/z*) 314 [M+H]⁺, 336[M+Na]⁺.

Compound 7S: To the anhydrous DMF (10 mL) was added (S)-oxazoline phenyl bromide **6** (1.5 g, 4.77 mmol), activated copper powder (1.5 g, 23.5 mmol). The mixture was heated under Ar at 145 °C for 24 h, and the solvent was removed in *vacuo*. To the residue was added CH₂Cl₂ (20 mL) and washed with aqueous ammonia (5%, 2×15 mL). The organic layer was separated and dried over Na₂SO₄ and evaporated in *vacuo*. The residue was purified through silica gel chromatography (CH₂Cl₂:EtOAc:THF=5:2:1) to give the mixture of **7S** with minor **7R** (1.04 g (93%) in 62% de (HPLC, C18-column, MeOH/H₂O=55/45, 1 mL/min, **7S**: Rt=25.7 min, **7R**: Rt=27.6 min). Recrystallization from the mixture of CH₂Cl₂ and light petroleum afforded **7S** in 99% de (0.513 g, 46%). mp. 162-163 °C. [α]_D²⁵ = -107 (c 0.036, EtOH), ¹H NMR (300 MHz, CDCl₃, δ ppm): 7.23(s,

2H, Ar-H), 5.99(d, 2H, J=1.2 Hz, OCH₂O), 5.95(d, 2H, J=1.2 Hz, OCH₂O), 4.25-4.15(m, 4H, oxazoline OCH₂), 3.95(s, 6H, OCH₃), 3.77-3.71(m, 2H, NCH), 1.20(d, 6H, J=3.2 Hz, CH₃); ¹³C NMR (75MHz, CDCl₃) 163, 147, 142, 136, 121, 111, 109, 101, 73, 61, 56, 21; ESI-MS(*m/z*) 469 [M+H]⁺. The CD spectroscopy showed the negative Cotton effect at 305 nm, 260 nm and positive Cotton effect at 293 nm in methanol.

(S)-DDB: To the solution of trifluoroacetic acid (0.20 mL, 2.50 mmol) in THF(15 mL) and water(0.5 mL) was added compound **7S**(0.40 g, 0.85 mmol). The mixture was stirred at r.t. overnight, and dried over Na₂SO₄. The solvent was removed in *vacuo*. To the residue was added CH₂Cl₂(20 mL), pyridine(2 mL), acetic anhydride(0.5 mL, 5.2 mmol) and 4-dimethylaminopyridine(5 mg, 0.04 mmol). The mixture was stirred at r.t. overnight. To the mixture was added methanol (5 mL), stirred at r.t. for 5 h, washed with 4% HCl(3×25 mL) and water (25 mL) and dried over Na₂SO₄. The solvent was removed in *vacuo* to obtain crude **8**. To the crude **8** was added methanol (10 mL), THF(10 mL) and NaOMe(0.25 g, 4.5 mmol), and stirred at r.t. overnight. The solvent was removed in *vacuo*. The residue was dissolved in CH₂Cl₂(20 mL) and washed with water. After the organic layer was dried over Na₂SO₄ and evaporated in *vacuo*, the residue was purified by silica gel column chromatography to afford (S)-DDB (0.26 g, 73%) in 93% ee (Chiral HPLC analysis: chiralcel OD column, ethanol/hexane=15/85, 0.5 mL/min). The CD spectroscopy of (S)-DDB exhibited negative Cotton effect at 259 nm. [α]_D²⁵ = -76.32 (c 0.41, CH₂Cl₂). mp. 140-142 °C. ¹H NMR(300 MHz, CDCl₃, δ ppm) 7.42 (s, 2H, 2Ar-H), 6.06(s, 4H, 2CH₂), 4.02(s, 6H, 2Ar-OCH₃), 3.78(s, 6H, COOCH₃). ESI-MS(*m/z*) 419 [M+H]⁺.

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