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New synthesis of (*S*)-dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-biphenyl-2,2′-dicarboxylate by configuration transform

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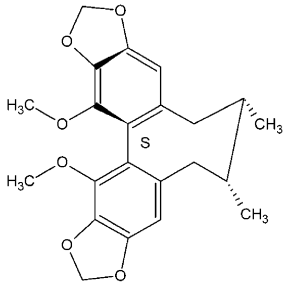
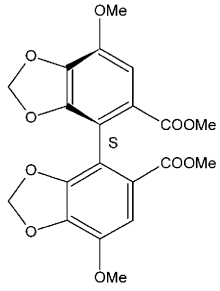
Abstract—(*R*/*S*)-4,4′-Dimethoxy-5,6,5′,6′-dimethenedioxy-2,2′-di-(4(*S*)-methyl-oxazoline-1)-biphenyl has been synthesized from dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-biphenyl-2,2′-dicarboxylate, and then the diastereoisomer mixture was almost fully converted to a single diastereoisomer with *S*-configuration ((*S*)-**3**) through the key configuration transform promoted by CuI, which was confirmed by CD, HPLC and ^{13}C NMR. The C_2-symmetric biphenyl, (*S*)-dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-biphenyl-2,2′-dicarboxylate was prepared easily via the hydrolysis and ester exchange of (*S*)-**3**.

The C_2-symmetric biaryl compounds bearing dioxazoline,[1] diphosphine and other functional groups are effective ligands for catalytic asymmetric reactions.[2] Biaryls from nature exhibit versatile biological activity. Biaryl compound, schizandrin C from *Schizandra chinesis* (Chinese wuweizi) shows various pharmacological activities,[3] especially anti-heptotoxic activity against liver injury induced by CCl_4. The substrate has been attracting considerable attention owing to its special structure and important biological properties. Dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-biphenyl-2,2′-dicarboxylate (**α-DDB, 1**), discovered by Xie et al.[4] in the course of synthesis of schizandrin C, almost show the same activity as schizandrin C. It was also demonstrated that both **α-DDB** and some of its derivatives exhibited anti-HIV activity.[5]

The four *ortho*-substituents of **DDB** made it difficult to rotate around aryl–aryl bond, which consequently resulted in two isomers. And each isomer showed different biological activity.[6] To date, there were rarely report on the preparation of chiral **α-DDB** besides classical resolution of **α-DDB**'s racemic isomers.[7] In the present letter, we reported new strategy to prepare optically pure (*S*)-DDB through the chiral oxazoline-mediated configuration transform of the biphenyl.[8]



Schizandrin C



(S)-DDB

(*S*)-**DDB** was prepared via (*S*)-4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-2,2′-di-(4(*S*)-methyl-oxazoline-1)-biphenyl ((*S*)-**3**) from **α-DDB**. Firstly, the key intermediate, (*S*)-**3** was prepared as Scheme 1. **α-DDB** was hydrolyzed to produce a corresponding biphenyl dicarboxylic acid, and then it was converted to the biphenyl dicarboxylic dichloride by the reaction with $SOCl_2$ in CH_2Cl_2. The biphenyl dicarboxylic dichloride was mixed with (*S*)-2-amino propanol to give biphenyl dicarboxylic diamide **2**[9] in 81% yield. Compound **2** reacted with $SOCl_2$ to yield corresponding dichloride, and then (*R*/*S*)-**3**[10] was obtained in 87% yield by heating the dichloride in the presence of potassium *tert*-butoxide in the mixed solvent of THF and *tert*-butanol at 70 °C. HPLC and ^{13}C NMR analysis[11] indicated a 50:50 diastereomeric ratio.

Keywords: Asymmetric; Biphenyl; Dioxazoline; CuI.
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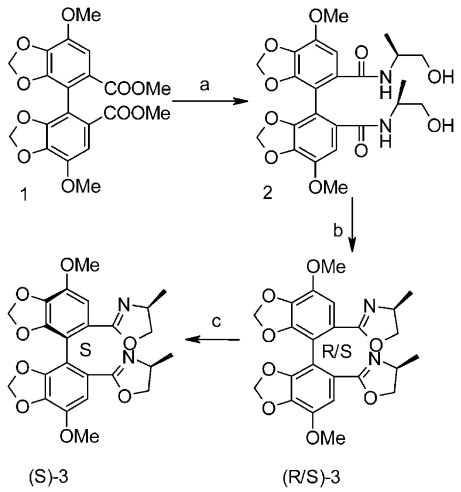


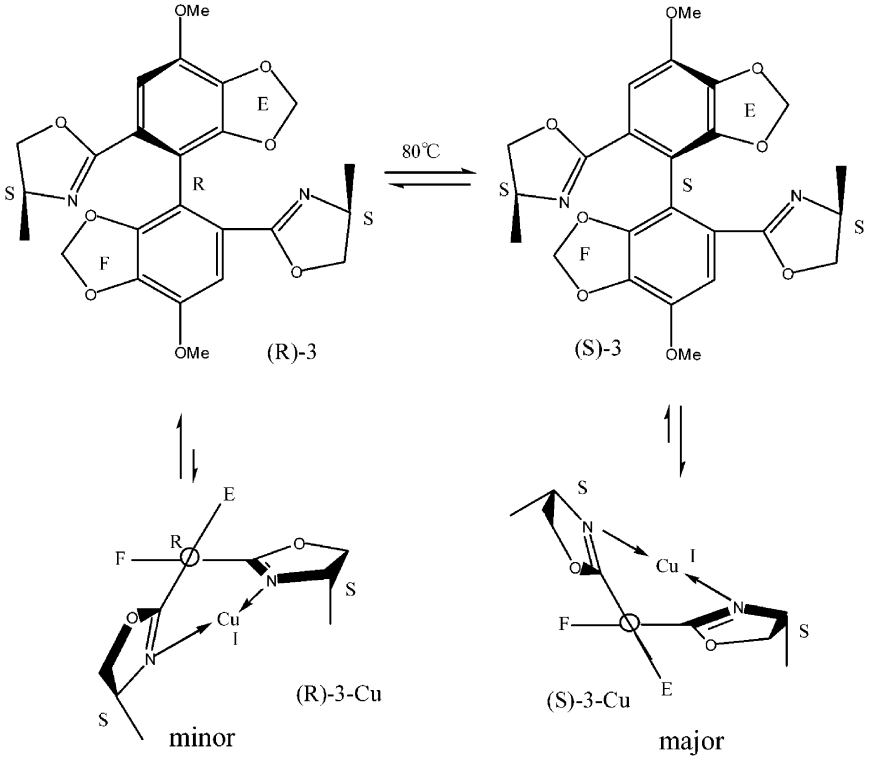
Scheme 1. Reagents and conditions: (a) 1. KOH, 3 equiv in 95% EtOH, reflux, 4 h; 2. concd HCl ; 3. $SOCl_2$, 3.0 equiv in CH_2Cl_2, rt, overnight; 4. (*S*)-2-aminopropanol 2.2 equiv Et_3N, in CH_2Cl_2, rt, 7 h; (b) 1. $SOCl_2$ 3.0 equiv Et_3N; 2. *t*-BuOK, 2.1 equiv, *t*-BuOH/THF, reflux, 8 h; (c) CuI 1.1 equiv, toluene, 80 °C, 20 h.

The mixture of the (*R*/*S*)-**3** and CuI was heated in dry toluene under Ar at 80 °C for 20 h. After cooling, the mixture was washed with 5% aqueous ammonia and water, and dried with Na_2SO_4, the solvent was removed in vacuo, and optically pure (*S*)-**3**[12] was afforded in 97% yield. HPLC and ^{13}C NMR analysis[11] indicated the ratio of diastereomers was 99.5:0.5.

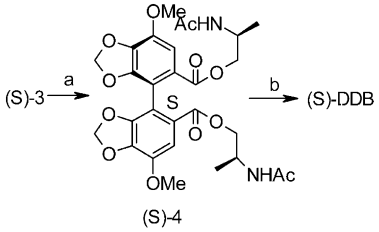
The circular dichroism (CD) spectroscopy of (*S*)-3 exhibited negative Cotton effect at 305 nm and 260 nm, and positive Cotton effect at 293 nm. On the basis of ORD curve it was deduced that there was another positive Cotton effect at the wavelength shorter than 240 nm. The four characteristic Cotton effect at about 305 nm, 293 nm, 260 nm and less than 240 nm corresponded to a negative–positive–negative–positive in sequence, and particularly the negative Cotton effect at about 260 nm followed by a positive Cotton effect at wavelength less than 240 nm can be served as evidence for the *S*-configuration of the biphenyl subunit in (*S*)-**3**.[13] In addition, it was also proven by the specific rotation.[12]

Diastereomeric mixture (*R*/*S*)-**3** was converted to complex (*S*)-**3**-Cu as Scheme 2, which was not only owing to the intramolecularly steric effect between the two methyls of chiral oxazolines, but also due to the interaction between Cu(I) with N atoms of bis-oxazolines. Complex (*S*)-**3**-Cu should dominated over (*R*)-**3**-Cu because there was less spacial repulsion, besides the distance between Cu(I) and the two N atoms of oxazoline rings was shorter in (*S*)-**3**-Cu than in (*R*)-**3**-Cu, which prefered to the formation of (*S*)-3-Cu complex. Thus, (*S*)-**3** combined with CuI to produce (*S*)-**3**-Cu, and the decrease of (*S*)-**3** led to the equilibrium between (*R*)-**3** and (*S*)-**3** towards (*S*)-**3** at 80 °C. As a result, almost all the (*R*/*S*)-**3** was used to form (*S*)-**3**-Cu.

In fact, the aforementioned configuration transform was different from the transform of the binaphthyl.[14] More important was that the configuration of (*S*)-**3** kept constant at room temperature after the separation of Cu(I) from the (*S*)-**3**-Cu complex. Furthermore, it was also found that the ratio 50:50 of (*S*)-**3** to (*R*)-**3** held constant through HPLC and ^{13}C NMR analysis after the diastereomeric mixture (*R*/*S*)-**3** was heated in DMSO.



Scheme 2.



Scheme 3. Reagents and conditions: (a) 1. TFA, 2.5 equiv water 2.2 equiv at rt, overnight. 2. Ac_2O 2.2 equiv, DMAP, 0.04 equiv at rt, overnight; (b) NaOMe, 0.2 equiv in MeOH at rt, overnight.

Secondly, (*S*)-DDB could be prepared as Scheme 3. (*S*)-**3** was hydrolyzed in THF with TFA and water and then the product reacted with acetic anhydride under catalysis of DMAP in pyridine at room temperature, and the crude diester diamide (*S*)-**4** was afforded. After (*S*)-**4** was alcoholysized in methanol in the presence of sodium methoxide at room temperature, (*S*)-dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-biphenyl-2,2′-dicarboxylate[15] was obtained in 85% yield in two steps.

In summary, we have found an efficient method to prepare (*S*)-DDB. (*S*)**-3** was prepared through configuration transform in excellent yield promoted by interaction between chiral oxazolines moiety of biphenyl and Cu(I). The stable (*S*)-**3** was conveniently transformed to (*S*)-DDB. Additionally, the application of (*S*)-**3** as a chiral ligand of catalytic asymmetric reactions was under study.

References and notes

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9. Biphenyl dicarboxylic amide **2** mp 234 °C, $[\alpha]_D^{25}$ −15.8° ($c = 1.53$, CH_3OH), ^1H NMR (300 MHz, DMSO-d_6) δ 8.17, 8.14 each (s, 1H, OH), 6.83, 6.78 each (s, 1H, Ar-H), 6.00, 5.84 each (s, 2H, OCH_2O), 3.97 (t, 1H, $J = 7.5$, OCH_2), 3.88, 3.87 each (s, 3H, OCH_3), 3.74–3.69 (m, 2H, 2NCH), 3.24–3.20 (m, 1H, CH), 3.18–3.12 (m, 1H, CH), 3.10–3.07 (m, 1H, CH), 2.80–2.78 (m, 1H, CH), 0.92 (d, 3H, $J = 6.6$, CH_3), 0.80 (d, 3H, $J = 6.6$, CH_3); IR 3280, 1616, 1553 cm^{-1}. ESI-MS 505 $[M+H]^+$.
10. (*R*/*S*)-**3** mp 171–172 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (s, 2H, Ar-H), 5.99 (d, 2H, $J = 1.2$, OCH_2O), 5.95 (d, 2H, $J = 1.2$, OCH_2O), 4.25–4.15 (m, 4H, oxazoline OCH_2), 3.95 (s, 6H, $2OCH_3$), 3.77–3.71 (m, 2H, 2NCH), 1.19 (d, 6H, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 163, 147, 142, 136, 121, 111, 109, 101, 73, 61, 56, 21; ESI-MS 469 $[M+H]^+$.
11. HPLC, column ODS C18, MeOH/H_2O = 55/45, 1 mL/min, (*S*)-**3**: rt = 25.7 min, (*R*)-**3**: rt = 27.6 min. Diastereomeric ratio was also calculated through peak intensity in ^{13}C NMR.
12. (*S*)-**3**: mp 172–173 °C, $[\alpha]_D^{25} = -289°$ ($c = 0.36$, in CH_2Cl_2).
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15. (*S*)-DDB: $[\alpha]_D^{25} = -76.3°$ ($c = 0.36$, CH_2Cl_2). Mp 140–142 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 2H, ArH), 6.06 (s, 4H, $2CH_2$), 4.01 (s, 6H, $2ArOCH_3$), 3.80 (s, 6H, $2CH_3$). ESI-MS 419 $[M+H]^+$.