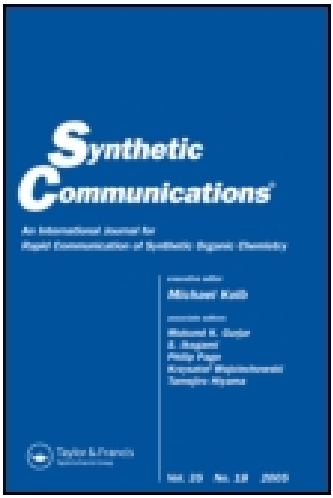

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Asymmetric Synthesis of β-DDB Through Oxazoline-Mediated Ullmann Coupling

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Abstract: Biphenyl lignan (β-DDB) (**2**), an effective drug in the treatment of hepatitis, was for the first time asymmetrically synthesized via a chiral oxazoline mediated Ullmann coupling. The two enantiomers of β-DDB have been obtained in this way by using the optically pure amino alcohols L-valinol and D-valinol, respectively. However, attempts to synthesize enantiopure α-DDB (**1**) by the same method failed because of the racemization of **1** at room temperature in solution.

Keywords: Asymmetry, biphenyl diester, bis(oxazoline), coupling, oxazoline

INTRODUCTION

The fruit of *Schizandra chinensis* has been used as drug in traditional Chinese medicine for a long time. Several pharmacologically active lignans have been isolated from the fruit[1–3] and *Schizandrin* C is the most potent one. The biphenyl unit in these lignans is crucial for their biological and medical activities. α-DDB (**1**), an intermediate formed in the total synthesis of *schizandrin* C, has attracted much attention in hepatitis therapy. Furthermore, several of its derivatives show potent anti-HIV effects.[4] During the total synthesis of α-DDB, its regioisomer β-DDB (**2**) was obtained as a by-product.[5,6] The biphenyl unit of β-DDB is identical to that of *schizandrin* C and has proved to be more active than α-DDB in the treatment of hepatitis and for the

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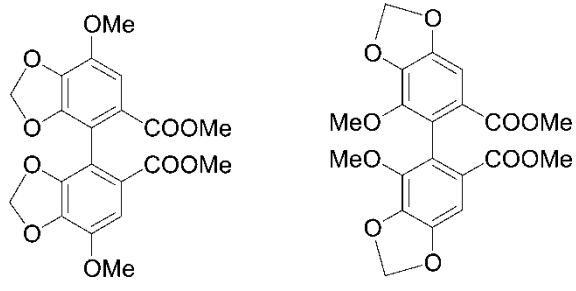
protection against liver damages. Furthermore, it also show potent anti-HIV effects.[7] Compounds **1** and **2** are chiral molecules because of the rotational restriction about the biphenyl axis, and they have been resolved by HPLC method (in the case of **1** also by chemical methods).[8–11] However, no asymmetric synthesis has been reported so far. We are interested in the pharmacological effects of the enantiomers of **2** and, therefore, we decided to develop a practical method for the preparation of enantiopure **2** (Figure 1).

In 1993, Nelson and Meyers[12–14] described a successful stereoselective Ullmann reaction, which employs a chiral oxazoline as the chiral controller, and excellent results were obtained. Using this methodology, several enantiopure biphenyl bisoxazolines have been successfully prepared that can be easily transformed into other useful functional groups.[15–17] However, the amino alcohols used in the synthesis of the chiral oxazolines were all derived from natural L-amino acids, which led to only one diastereisomer of the chiral bis(oxazoline) was formed.

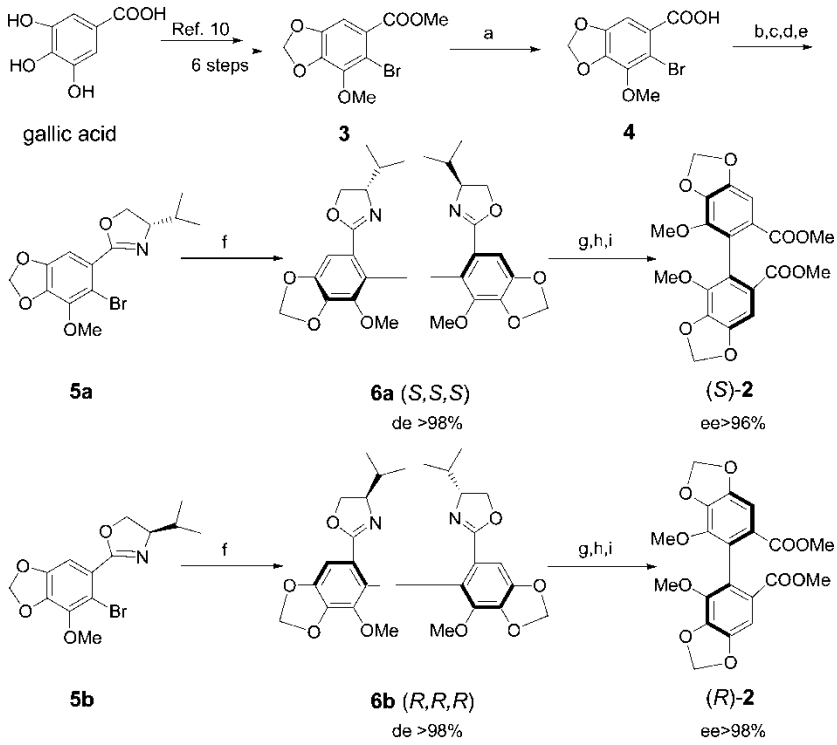
Here both L-valinol and D-valinol were used to synthesize the corresponding chiral oxazolines **5a** and **5b**, followed by asymmetric Ullmann coupling based on Nelson and Meyers' method to yield **6a** and **6b**, which can then be transformed to (S) and (R)-β-DDB (**2**) with up to 98% e.e. (Scheme 1).

We chose **3** as the starting material, which was the intermediate in the total synthesis of racemic **2** from gallic acid.[10] Hydrolysis of **3** afforded **4**, which was then treated with $SOCl_2$ to furnish the corresponding acid chloride. The latter was treated with L-valinol[18] and Et_3N to afford the corresponding amide alcohol, which was then reacted with $SOCl_2$ followed by reflux with 0.5 M of NaOH in MeOH-H_2O to give the oxazoline **5a**. While using D-valinol, **5b** was obtained. Treatment of **5a** and **5b** with activated copper[19] in refluxing anhydrous DMF for 48 h gave the enantiopure bisoxazoline **6a** and **6b**, respectively. Compounds **6a** and **6b** were reacted with trifluoroacetic acid and Na_2SO_4 followed by acetic anhydride in the presence of pyridine to provide the ester amides. Transesterification of the latter



1 **2**

Figure 1. **1** (α-DDB) and **2** (β-DDB).

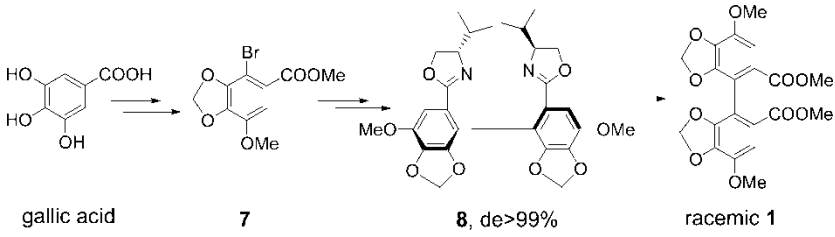


Scheme 1. Reagents and conditions: a) 5% KOH, reflux for 2 h; b) $SOCl_2$; c) L-valinol or D-valinol, Et_3N; d) $SOCl_2$; e) 2% NaOH, MeOH: $H_2O = 1:1$, reflux, 2 h; f) activated Cu, DMF, reflux, 40 h; g) TFA, Na_2SO_4; h) Ac_2O, Py; and i) NaOMe, MeOH, rt, 20 h.

using methanolic NaOMe at rt led to give the corresponding **(S)-2** and **(R)-2**, respectively.

The e.e. of **(S)-2** and **(R)-2** was determined by HPLC using a commercial chiral OD column, and their configuration was assigned according to Ref. 10 Therefore, **6a** and **6b** are assigned as (**S, S, S**) and (**R, R, R**). The results are in accordance with that described by Nelson and Meyers.[12–14]

We also attempted to synthesize the enantiopure α-DDB (**1**) by Nelson and Meyers' method; however, only racemic **1** was obtained (Scheme 2). Although high diastereoselectivity (>99% de) has been achieved via asymmetric Ullmann coupling, unfortunately racemization occurs in the course of the transformation of the bisoxazoline **8** to the corresponding ester.[20,21] The racemization may be attributed to the smaller sterical hindrance of the methylenedioxyl group in **1** than that of the methoxy group in **2**, which leads to easy rotation around the biphenyl axis. To clarify this, the enantiopure α-DDB obtained by resolution of racemic α-DDB using enantiopure



Scheme 2.

α-methylbenzylamine as resolving reagent was dissolved in chloroform or methanol and complete racemization was observed within 24 h under room temperature. However, no racemization was observed in the solid state even when stored at room temperature for several months.

In conclusion, the diasteromerically pure bisoxazolines **6a** and **6b** have been successfully synthesized by chiral oxazoline–mediated Ullmann coupling and transformed to enantiopure β-DDB (**2**) in up to 98% e.e. The attempt to synthesize the enantiopure α-DDB (**1**) failed, although the corresponding bisoxazoline **8** can be obtained in 99% d.e. using the same method. Racemization occurs in the course of the transformation of bisoxazoline **8** to α-DDB (**1**).

EXPERIMENT

Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on Bruker DRX-500 (500 MHz) and AV-300 (300 MHz) instruments. Elemental analyses were performed on Vario equipment. Optical rotations were measured on Wzz-1 apparatus. IR spectra were recorded on a Bruker Equinox55 instrument. Mass spectra were recorded on Micromass GCT mass spectrometer. The enantiomeric purities of **2** were assessed by HPLC using a Diacel Chiral OD column. All the reagents were used as purchased except when stated otherwise. Compounds **3** and racemic **2** were prepared as reported.[10] L-valinol and D-valinol were synthesized from L-valine and D-valine.[18]

6-Bromo-7-methoxy-benzo[1,3]dioxole-5-carboxylic acid (4).[7] A suspension of **3** (24.7 g, 85.4 mmol) in 5% KOH (600 ml) was heated to reflux for 2 h. The solution was cooled and acidified by hydrochloric acid. The precipitate formed was collected by filtration, washed with water, and dried at 100°C. **4** was obtained as white solid. Yield: 23.0 g (98%). Mp 181–183°C. ^{1}H NMR (300 MHz, d_6-acetone): δ 3.78 (s, 3H), 6.02 (s, 2H), 7.08 (s, 1H).^{13}C NMR (300 MHz, d_6-acetone): 57.1, 101.2, 104.5, 109.5, 125.4, 141.0, 148.5, 152.2, 172.0. Anal. calcd. for $C_9H_{10}BrO_5$: C, 39.30; H, 2.57; Found: C, 39.25; H, 2.55.

(S)-2-(6-Bromo-7-methoxy-benzo[1,3]dioxol-5-yl)-4-isopropyl-4,5-dihydro-oxazole (5a) and (R)-2-(6-Bromo-7-methoxy-benzo[1,3]dioxol-5-yl)-4-isopropyl-4,5-dihydro-oxazole (5b). To 8.26 g (30.0 mmol) of **4** was added $SOCl_2$ (60 ml), and the mixture was heated to reflux for 3 h. After excess $SOCl_2$ was removed in vacuo, the resulting light-yellow solid was dissolved in 150 ml of CH_2Cl_2 and added to a solution of 3.56 g (34.6 mmol) of L-valinol[18] and Et_3N (9.6 ml, 69 mmol) in 120 ml of CH_2Cl_2 cooled to 0°C. The mixture was stirred overnight, diluted by another 200 ml of CH_2Cl_2, then washed with 2 N HCl and brine, and dried (Na_2SO_4). The solution was cooled below 0°C and then a solution of 8 ml of $SOCl_2$ in 50 ml of CH_2Cl_2 was added dropwise. The mixture was stirred overnight and again cooled to 0°C 10 ml of water and saturated Na_2CO_3 solution were added. Then, the solution was separated, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The residue was added to 120 ml of MeOH and 4.8 g of NaOH in 120 ml of water and then heated at reflux for 5 h. After cooling, MeOH was evaporated and the mixture was extracted with CH_2Cl_2 (3×100 ml). The CH_2Cl_2 phase was washed with brine, dried (Na_2SO_4), and filtered. Removing the CH_2Cl_2 gave light-yellow oil, which proved to be **5a** and was pure enough for subsequent use. Yield: 8.27 g, 80%. $[\alpha]_D^{20} = -40.4$ (c 2.0, EtOH). IR (KBr): 1655 (C═N). ^{1}H NMR (300 MHz, $CDCl_3$): δ0.90 (d, $J = 6.8$ Hz, 3H), 1.0 (d, $J = 6.8$ Hz, 3H), 1.86 (m, 1H), 3.99 (s, 3H), 4.06–4.15 (m, 2H), 4.39 (m, 1H), 5.99 (s, 2H), 6.86 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$): 17.9, 18.5, 32.5, 60.0, 70.3, 72.6, 102.0, 105.3, 108.1, 124.2, 139.2, 140.7, 148.2, 162.6. Anal. calcd. for $C_{14}H_{16}BrNO_4$: C, 49.14; H, 4.71; N, 4.09; Found: C, 49.10; H, 4.78; N, 4.12. FAB-MS (m/z): 341.

5b: Prepared as **5a** from **4**. Yield: 77%. $[\alpha]_D^{20} = +42.0°$ (c 2.0, EtOH). Anal. calcd. for $C_{14}H_{16}$ $BrNO_4$: C, 49.14; H, 4.71; N, 4.09; Found: C, 49.15; H, 4.72; N, 4.11. Spectra are identical to **5b**.

(S, S, S)-4,4′-Dimethoxy-[5,5′]bi[benzo[1,3]dioxolyl]-6,6′-bis(4-isopropyl-4,5-dihydro-oxazole) (6a) and (R, R, R)-4,4′-Dimethoxy-[5,5′]bi[benzo[1,3]dioxolyl]-6,6′-bis(4-isopropyl-4,5-dihydro-oxazole) (6b). The mixture of 8.27 g (24.2 mmol) of the bromo oxazoline **5a**, 8.8 g of activated copper powder,[19] and 18 ml of dry DMF was heated to 110°C for 3 h under a nitrogen atmosphere. Then, additional 50 ml of DMF was added and the mixture was heated to reflux for 48 h. After cooling, the mixture was diluted with 300 ml of CH_2Cl_2 and washed with 5% aqueous ammonia (3×150 ml) and brine (2×100 ml), and dried (Na_2SO_4). After the solvent was removed, the residue was subjected to column chromatography (petroleum ether–EtOAc = 5 : 1, neutral Al_2O_3) to give a light-yellow solid. After it was recrystallized from petroleum ether (50 ml) and EtOAc (5 ml), 3.88 g of diastereomerically pure bis(oxazoline) **6a** was obtained as a white needle crystal. Yield: 65%. Mp 108–111°C; $[\alpha]_D^{20} = -70.3$ (c 0.8, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, $J = 6.8$ Hz, 6 H), 0.84 (d, $J = 6.8$ Hz, 6H),

1.55–1.62 (m, 2H), 3.76 (s, 6H), 3.64–3.84 (m, 4H), 4.06 (m, 2H), 5.99 (s, 4H), 7.10 (s, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): 18.3, 18.8, 32.8, 59.8, 70.2, 72.6, 101.5, 104.0, 122.5, 125.3, 138.8, 141.5, 148.2, 163.2. IR (KBr): 1652 cm^{-1}(C═N). Anal. calcd. for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34; Found: C, 64.08; H, 6.18; N, 5.32. FAB-MS (m/z): 524.

6b: Prepared as **6a** from **5b.** Yield: 62%.Mp 105–107°C. $[\alpha]_D^{20} = +68.8$ (c 1.2, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (d, $J = 6.8$ Hz, 6H), 0.82 (d, $J = 6.8$ Hz, 6H), 1.55–1.62 (m, 2H), 3.78 (s, 6H), 3.58–3.76 (m, 4H), 4.09(m, 2H), 6.01(s, 4H),7.15 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): 18.3, 18.9, 31.8, 59.8, 71.2, 72.2, 101.8, 104.2, 122.6, 125.7, 138.9, 141.7, 148.3, 163.5; IR (KBr): 1652 cm^{-1} (C═N); Anal. calcd. for $C_{28}H_{32}N_2O_8$: C, 64.11; H, 6.15; N, 5.34; Found: C, 64.18; H, 6.15; N, 5.37. FAB-MS (m/z): 524.

(S)-4,4′-Dimethoxy-[5,5′]bi[benzo[1,3]dioxolyl]-6,6′-dicarboxylic acid dimethyl ester (S-2) and (R)-4,4′-Dimethoxy-[5,5′]bi[benzo[1,3]dioxolyl]-6,6′-dicarboxylic acid dimethyl ester (R-2). To the bis(oxazoline) **6a** (2.0 g, 3.8 mmol) was added THF (200 ml), H_2O (4.5 ml), trifluoroacetic acid (6.0 ml, 78.4 mmol), and Na_2SO_4 (20 g). The mixture was stirred vigorously overnight. Additional Na_2SO_4 was added to ensure anhydrous conditions and then the solvent was removed below 45°C. The resultant colorless liquid was added to 150 ml of CH_2Cl_2, 10 ml of Ac_2O, and 10 ml of pyridine. The reaction was stirred at rt for 2 days. Then the mixture was diluted to 300 ml, washed with 2 N of HCl (3 × 100 ml) and brine (2 × 100 ml) and dried (Na_2SO_4). After removing the solvent, a white solid was obtained. To the solid was added an NaOMe solution prepared by the dissolution of sodium (3.0 g, 13 mmol) in methanol (120 ml). After stirring at rt for 5 h, a white precipitation formed. The mixture was neutralized with methanolic acetic acid and the solvent was removed by rotary evaporation. The residue was added to 100 ml of water and extracted with CH_2Cl_2 (2 × 80 ml). The extraction was washed with brine and dried (Na_2SO_4). After removal of the solvent, the residue was purified by silica-gel chromatography with petroleum ether–EtOAc–CH_2Cl_2 (7 : 2 : 1) as eluent to give **2** as a white solid, 1.2 g, 75.5%. Mp 206–208°C (lit.[10] 207–208°C); $[\alpha]_D^{20} = -42.2°$ (c 1.2, $CHCl_3$); e.e. = 96.5%. Chiral HPLC analysis: chiral OD column, 1.0 ml/min, 8 : 2 hexane–isopropanol, $\lambda = 254$ nm, t_R(S) = 21.2 min; ^{1}H NMR(300 MHz, d_6-acetone) δ 3.56(s, 3H), 3.71 (s, 3H), 6.15 (s, 4H), 7.12 (s, 2H).

R-2: Prepared from **6b** as **S-2**. Yield: 69%. Mp 206–207°C (lit.[10] 207–208°C); $[\alpha]_D^{20} = +43.2°$ (c 1.5, $CHCl_3$). E.e. (98%). Chiral HPLC analysis: t_R (R) = 11.2 min. Spectra are identical to **S-2**.

The resolution of α-DDB (1) and research on the racemization of enantiopure 1. A suspension of 8.36 g (20 mmol) of **1** was hydrolyzed to its diacid according to Ref. 22 and then the diacid was suspended in 50 ml

of EtOH and 6 ml of H_2O, heated to 60°C and 5 ml (40.0 mmol) of L-(−)-α-benzylethyl amine in 10 ml of EtOH was added. After the addition, the mixture turned clear and was cooled to rt, and a colorless crystal formed gradually overnight. The crystals were collected, washed with EtOH, and recrystallized from EtOH twice yielding 4.1 g of colorless crystals. The crystals were dissolved in 30 ml of H_2O and the solution was acidified with HCl. A white solid precipitated immediately, which was collected by filtration and washed with water. The optically active biphenyl dicarboxylic acid was obtained with $[\alpha]_D^{20} = -83$ (c 1.5, C_5H_5N) and mp 263°C (lit.[8] 260–262°C). The acid was dissolved in saturated Na_2CO_3 and 2.0 ml of dimethyl sulfate was added. A white solid formed immediately and the mixture was stirred for 1 h. The solid was filtered and washed with water to give 1.5 g of (−)-α-DDB **1**. $[\alpha]_D^{20} = -81$(c 0.5, $CHCl_3$) [lit.[8] $[\alpha]_D^{21} = -78.60$ (c 0.52, $CHCl_3$)]. Mp178–179°C (lit.[5] 179–181°C); e.e. = 95%. The e.e. was assessed by HPLC method: chiral OD column, 1.0 ml/min, 8 : 2 hexane–isopropanol, $\lambda = 254$ nm. ^{1}H NMR (300 MHz, CDCl3):δ 3.67 (s, 6H), 3.96 (s, 6H), 5.99 (s, 4H), 7.37 (s, 2H).

Racemization of (−)-α-DDB **1** in $CHCl_3$ has also been studied. A solution of (−)-α-DDB **1** in $CHCl_3$ with a rotation $[\alpha]_D^{20} = -81$ (c 0.5, $CHCl_3$) was put at 20°C. After 28 h the rotation turned to 0. The racemization in other solvents such as methanol was also observed. However, in the solid form no racemization has occurred when stored for several months.

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REFERENCES

1. Ikeya, Y.; Kanatani, M.; Hakozaki, M.; Taguchi, H.; Mitsuhashi, H. *Chem. Pharm. Bull.* **1988**, *36*, 3974.
2. Chen, Y. Y.; Shu, Z.; Li, L. *Scientia Sinica* **1976**, *19*, 276.
3. Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 1383.
4. Chen, D. F.; Zhang, S. X.; Xie, L.; Xie, J. X.; Chen, K.; Kashiwada, Y.; Zhou, B. N.; Wang, P.; Cosentino, L. M.; Lee, K. H. *Bioorg. Med. Chem.* **1997**, *5*, 1715.
5. Xie, X. J.; Zhou, J.; Zhang, C. Z. *Acta. Pharm. Sinica* **1982**, *17*, 23.
6. Xie, J. X.; Zhou, J.; Zhang, C. Z. *Scientia Sinica* **1983**, *26*, 1291.
7. Guo, R. Y.; He, J.; Chang, J. B.; Chen, R. F.; Xie, J. X.; Ge, Y. H.; Liu, Y. Q. *Chem. J. Chinese Universities* **2001**, *22*, 2018.
8. Zhang, C. Z.; Zhan, S. L.; Xie, J. X. *Kexue Tongbao* **1986**, *32*, 72.
9. Yeng, F. W.; Chiu, J. Y.; Wang, C. L. Method for Resolving Racemic Compounds. US Patent 5, 504, 221 April 2, 1996.

10. Chang, J. B.; Chen, R. F.; Guo, R. Y.; Dong, C. H.; Zhao, K. *Helv Chim. Acta.* **2003**, *86*, 2239.
11. Liu, Q. Y.; Ge, Y. H.; Cai, Q. S.; Jiang, S. X.; Chen, L. R.; Chang, J. B. *Chem. J. Chinese Universities* **2000**, *21*, 1828.
12. Nelson, T. D.; Meyer, A. I. *J. Org. Chem.* **1994**, *59*, 2577.
13. Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061.
14. Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259.
15. Meyers, A. I.; Willemsen, J. *J. Tetrahedron* **1998**, *54*, 40493.
16. Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655.
17. Meyers, A. I.; Willemsen, J. *J. Tetrahedron Lett.* **1996**, *37*, 791.
18. Mckennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568.
19. Fuson, R. C.; Cleveland, A. *Organic Syntheses*. Wiley: New York, 1955; Collect. Vol. 3; p. 339.
20. Levin, J. I.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 2347.
21. Meyers, A. I.; Slade, J. J. *J. Org. Chem.* **1980**, *45*, 2785.
22. Chang, J. B.; Xie, J. X. *Acta Pharm Sinica* **1998**, *33*, 424.