Chinese Chemical Letters Vol. 12, No. 3, pp. 189–192, 2001

First Enantioselective Synthesis of (2R, 3R)- and (2S, 3S)-2-(4-hydroxyphenyl)-3-hydroxymethyl-1, 4-benzodioxan-6-carbaldehyde

Wen Xin GU, Xiao Bi JING, Xiao Chuan CHEN, Xin Fu PAN*

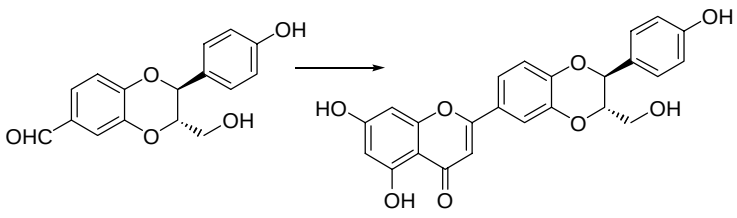
Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000

Abstract: A novel enantioselective synthetic approach to 1,4-benzodioxane lignans was reported in which (2R, 3R)- and (2S, 3S)-2-(4-hydroxyphenyl)-3-hydroxymethyl-1, 4-benzodioxan-6-carbaldehyde were first synthesized.

Keywords: Enantioselectivity, synthesis, 1,4-benzodioxane, lignans.

Numerous lignans containing 1,4-benzodioxane nucleus represent a class of natural products with cytotoxic and hepatoprotective activities[1,2]. Recently we have reported the racemic total synthesis of sinaiticin, a flavonolignan of the 1,4-benzodioxane type which was isolated from sinaiticum leaves found in sinai region of Egypt, using 2-(4-hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde as the key interme-diate[3,4]. This species exhibits significant inhibitory activity against the murine lymphocytic leukaemia P-388 cell line[3]. An unsolved problem in this area was the asymmetric synthesis of the chiral 1,4-benzodioxane moiety[5]. In continuation of our studies on the total synthesis of 1,4-benzodioxane lignans, we now report the first enantioselective synthetic approach to the key intermediate (2R, 3R)- and (2S, 3S)-2-(4-hydroxyphenyl)-3-hydroxymethyl-1,4-benzodioxan-6-carbaldehyde (**Scheme 1**). This kind of 1,4-benzodioxan-carbaldehydes have been used as synthetic building blocks for the synthesis of natural 1,4-benzodioxane lignans[6].

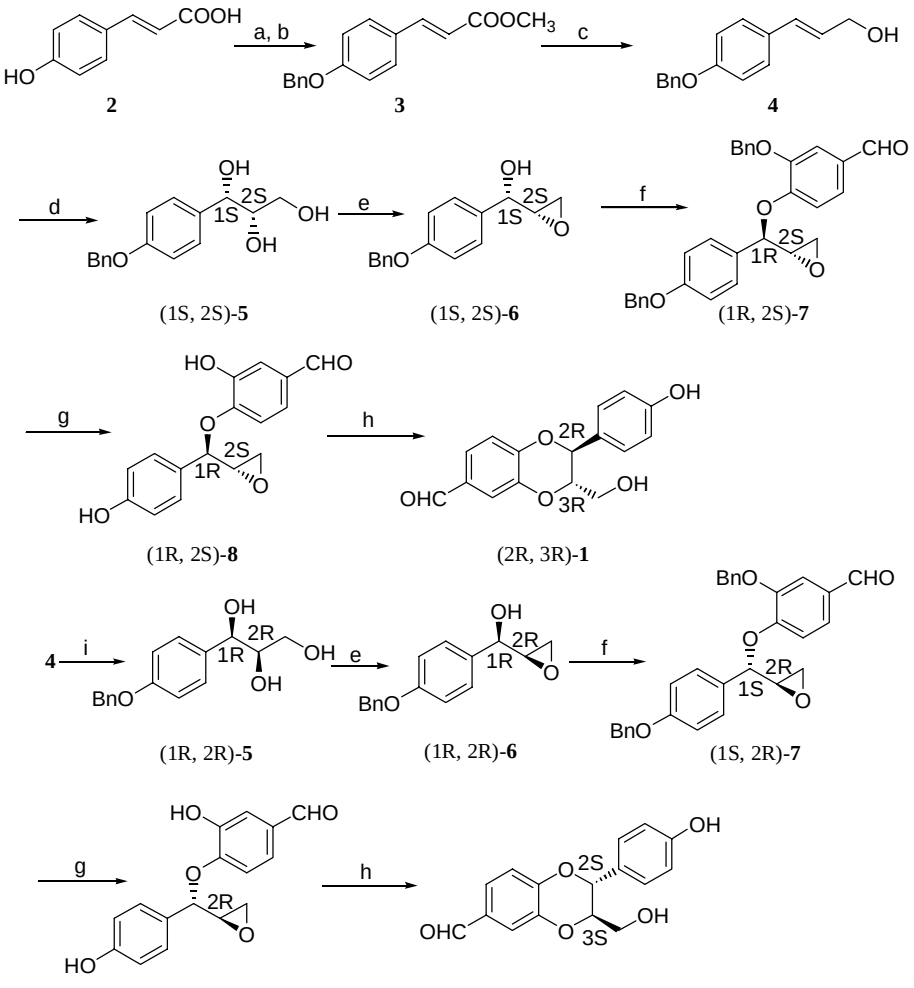
Scheme 1



1 Sinaiticin

As shown in **Scheme 2**, 4-hydroxycinnamic acid **2** was converted to a benzyl ether **3** in 90% yield by esterification with acidic methanol followed by treatment with benzyl chloride. Reduction of **3** gave the corresponding unsaturated alcohol **4** in 90% yield. Asymmetric dihydroxy reaction of **4** by AD-mix-α afforded (1S, 2S)-**5** in 91% e.e. and 86% yield[7]. (1S, 2S)-**5** was treated with *N* –tosylimidazole in dry THF to give oxirane (1S, 2S)-**6** in 72% yield[8]. Mitsunobu reaction between (1S, 2S)-**6** and 3-benzyloxy-4-

Scheme 2



(a) MeOH, H_2SO_4, 90 ^{0}C, 16 h. (b) BnCl, DMF, K_2CO_3, 160 ^{0}C, 3 h, (a and b 90%). (c) LAH, THF, -10 ^{0}C, 1 h, (90%). (d) AD-mix-α, *t*-BuOH, H_2O, 0 ^{0}C, 20 h, (86%). (e) *N*–tosylimidazole, NaH, THF, rt, 2 h, (72%). (f) DEAD, Ph_3P, 4-benzyloxy-3-hydroxybenzaldhyde, THF, rt, 24 h, (81%). (g). Pd/C (5%), H_2, EtOAc, rt, 6 h, (80%). (h) K_2CO_3, MeOH, rt, 1 h, (93%). (i) AD-mix-β, *t*-BuOH, H_2O, 0 ^{0}C, 20 h, (83%).

hydroxybenzaldhyde gave a characterized ether (1R, 2S)-**7** in 81% yield[9,10]. In this

reaction the absolute configuration of C_1-position was converted completely by a S_N2 nucleophilic displace of 3-benzyloxy-4-hydroxybenzaldhyde. The two benzyl groups of (1R, 2S)-**7** were removed by hydrogenolysis under atmospheric pressure of hydrogen in the presence of 5% palladized charcoal in ethyl acetate to afford (1R, 2S)-**8** in 88% yield while the epoxide moiety remained intact[5]. (1R, 2S)-**8** underwent cyclization with potassium carbonate to afford (2R, 3R)-**1** in 93% yield. In this reaction an intramolecular nucleophilic attack at C_2-position of oxirane by the phenol hydroxy in its potassium salt led to a complete conversion of the absolute configuration of C_2-position and the formation of 1,4-benzodioxane[11]. In the ^{1}H-NMR spectrum of (2R, 3R)-**1** the H-3 signal appeared as a doublet at δ 5.06 with a coupling constant J = 8.1 Hz, indicating a *trans* isomer and *threo* configuration. Similarly, asymmetric dihydroxy reaction of **4** by AD-mix-β afforded (1R, 2R)-**5** in 90% e.e. and 83% yield. (1R, 2R)-**5** was treated in the same four steps to afford (2S, 3S)-**1** in good yield.

Advantages of the synthetic approach included: i) 2-aryl- and 3-aryl-1,4-benzodioxane lignans can be synthesized regioselectively when 3-benzyloxy-4-hydroxybenzaldhyde and 4-benzyloxy-3-hydroxybenzaldhyde were used respectively, ii) SN_2 type nucleophilic displace on two chiral carbons led to the complete conversions of the absolute configuration of them, so the absolute configuration of 1,4-benzodioxane can be confirmed and *trans* isomers is the single product.

Acknowledgment

We are grateful to the National Natural Science Foundation of China (No. 29972015) for financial support.

References and Notes

1. L. –G. Zhuang, O. Seligmann, K. Jurcic, H. Wagner, *Planta Med.*, **1982**, *45*, 172.
2. H. Hikino, Y. Kiso, H. Wagner, M. Fiebig, *Planta Med.*, **1984**, *50*, 248.
3. S. Mohammed, A. M. Mamdouh, P. M. John, A. Douglas Kinghorn, *Photochemistry*, **1993**, *34*, 839.
4. X. G. She, X. B. Jing, X. F. Pan, *Tetrahedron Lett.*, **1999**, *40*, 4567.
5. E. Taniguchi, S. Yamauchi, S. Nagata, T. Ohnishi, *Biosci. Biotech. Biochem.*, **1992**, *56*, 630.
6. R. S. Ward, *Nat. Prod. Rep.*, **1997**, *14*, 43. **1999**, *16*, 75.
7. K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, D. Xu, X. L. Zhang, *J. Org. Chem.*, **1992**, *57*, 2768.
8. D. R. Hicks, B. Fraser-Reid, *Synthesis*, **1974**, 203.
9. H. Mitsunobu, *Synthesis*, **1981**, 1.
10. S. V. Kessar, Y. P. Guputa, T. Mohammad, M. Goyal, K. K. Sawal, *J. Chem. Soc., Chem. Commun.*, **1983**, 400.
11. T. Ganesh, G. L. David Krupadanam, *Syn. Common.*, **1998**, *28*, 3121.
12. (1R, 2S)-**8**: A white crystalline solid, mp 110-112 °C; $[\alpha]_D$ +12 (*c* 1.0, $CHCl_3$); ^{1}H-NMR (D_6-acetone, 400Hz): δ 2.82 and 2.87 (2dd, 12.2 Hz, 2.5 Hz, 2 H), 3.41 (m, 1 H), 5.35 (d, 4 Hz, 1 H), 6.80-7.43 (m, 7 H), 9.70 (s, 1H); MS (*m/z*): 286 (M^+ 30), 149 (34), 137 (100), 119 (13); Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.18; H, 4.95; IR (KBr/cm^{-1}): 3506, 3286, 3010, 2844, 1707, 1596, 1514, 1271, 1237.(1S, 2R)-**8**: A white crystalline solid, mp 129-131 °C; $[\alpha]_D$ -13 (*c* 1.0, $CHCl_3$); Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.20; H, 4.92; Other spectral data were the same as those of (1R, 2S)-**8**.
13. (2R, 3R)-**1**: A white solid. mp 147-148 °C; $[\alpha]_D^{25}$ + 28 (*c* 0.9, $CHCl_3$); ^{1}H-NMR (D_6-acetone,

400Hz): δ 3.47 and 3.72 (2dd, 12.5 Hz, 2.6 Hz, 2 H), 4.13 (m, 1 H), 5.06 (d, 8.1 Hz, 1 H), 6.68-7.47 (m, 7 H), 9.83 (s, 1 H); ^{13}C-NMR (D_6-acetone, 100Hz): 61.3, 77.5, 79.3, 115.8-131.7, 191.6; MS (*m/z*): 286 (M^+, 60), 268 (31), 232 (23), 149 (40), 137 (7), 107 (100); Anal.Calcd for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.10; H, 4.91; IR (KBr/cm^{-1}): 3480, 3207, 2911, 2857, 1743, 1603, 1499, 1274, 1215.

14. (2S, 3S)-**1**: A white solid. mp 117-119 °C; $[\alpha]_D^{25}$ -25 (*c* 0.9, $CHCl_3$); Anal. Calcd. for $C_{16}H_{14}O_5$: C, 67.12; H, 4.93. Found: C, 67.14; H, 4.92; Other spectral data were the same as those of (2R, 3R)-**1**.

Received 11 July, 2000