*Communication*

# Total Synthesis of (–)-Kaerophyllin, (–)-Hinokinin and (±)-Isohinokinin

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**A convenient and rapid approach for the syntheses of (–)-kaerophyllin (1), (–)-hinokinin (2) and (±)-isohinokinin (3) was described. The key steps were involved in condensation of aromatic aldehyde and alkylation of the resulting ester to give the complete skeleton of dibenzylbutyrolactone-lignan. Hydrolysis, followed by resolution with quinine, reduction and when appropriate, oxidation gave the title compound. The asymmetric total synthesis of the kaerophyllin (1) was reported for the first time.**

**Keywords** kaerophyllin, hinokinin, isohinokinin, quinine resolution

Kaerophyllin **(1)**, hinokinin **(2)** and their analogue-isohinokinin **(3)** belong to the dibenzylbutyrolactone-lignans. Kaerophyllin **(1)** was isolated from the root of spotted cow parsley (*Chaerophyllum maculatum Willd.*)[1] and hinokinin **(2)** was isolated from the heartwood of Libocedrus formosana Florin.[2] According to MacRae and Towers,[3] a five membered lactone ring and a methylenedioxyl group were important structural characteristics which contribute to the activity of lignans as antitumor agents. Moreover, an unsaturated double bond between $C_3$—$C_6$ is associated with the stronger cytotoxicity. In addition, the series of lignans has antiviral activity and specifically inhibits certain enzymes. Because of their biological activities Much interest has been focused on their investigation of the possible mechanism for cell-growth suppression of cancer cells.[4] Some synthetic methods of dibenzylbutyrolactone-lignan have been reported.[5,6] Kise *et al.*[7] reported the first asymmetric synthesis of (–)-hinokinin **(2)** by the oxidative homocoupling of (4*S*)-3-(3-arylpropanoyl)-4-isopropyl-2-oxazolidinones with LDA-$TiCl_4$. Lu[8] utilized cyclization of acyclic 2-alkenyl 2-alkynoate to construct the γ-butyrolactone, further functionalized to prepare (±)-isohinokinin **(3)**. All of them involved in the expensive reagents and rigorous experimental conditions. Herein, a rapid and efficient method for the synthesis of unsaturated and saturated dibenzylbutyrolactone-lignan was reported.

As shown in Scheme 1, condensation of aromatic aldehyde **4a** or **4b** with diethyl succinate via Stobbe reaction, followed by esterification, afforded the corresponding diester **5a** (90%) or **5b** (92%) in good yield. Transformation of **5a** or **5b** into the corresponding anion via LDA, followed by alkylation with 3,4-methylenedioxyb gave the unsaturated diester **6a** (90%) or **6b** (89%). Hydrolysis of **6a** or **6b** provided diacid **7** in nearly quantitative yield. At this stage, resolution of **7** via the quinine salt gave (–)-**7a** (43%) or (–)-**7b** (40%). The absolute configuration of these acids follows from their relationship with the final products of the synthesis. Esterification of (–)-**7a** or (–)-**7b** with diazomethane or ethanol/benzene produced the corresponding diester (–)-**8a** (98%) or (–)-**8b** (90%). In Scheme 2, treatment of (–)-**8a** with $LiAlH_4$/$AlCl_3$ afforded the diol (+)-**9** in 92% yield, which was oxidized with $MnO_2$ to give (*R*)-(–)-kaerophyllin **(1)** in 86% yield.[9] On the other hand, hydrogenation of the diester (–)- **8b** under hydrogen atmosphere (Pd/C 10%,

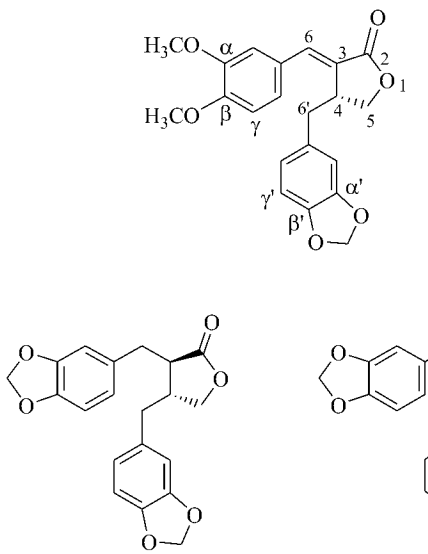

**Fig. 1** Structurs of (–)-kaerophyllin **(1)**, (–)-hinokinin **(2)** and (±)-isohinokinin **(3)**.

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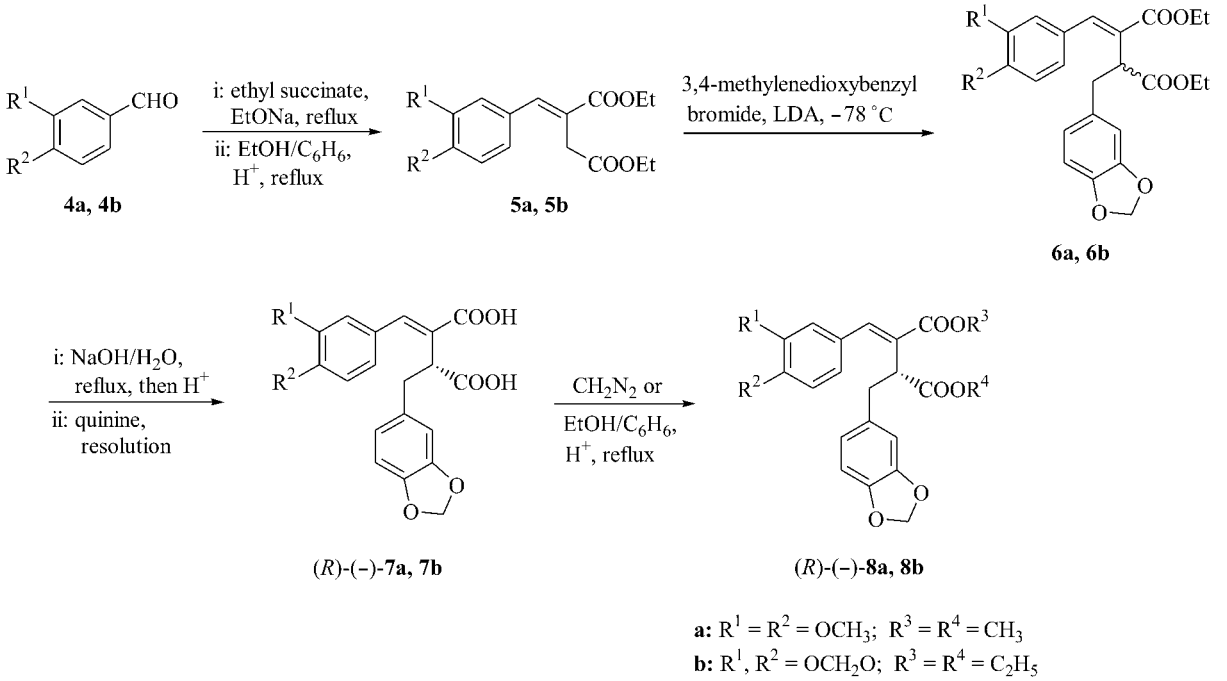
**Scheme 1**

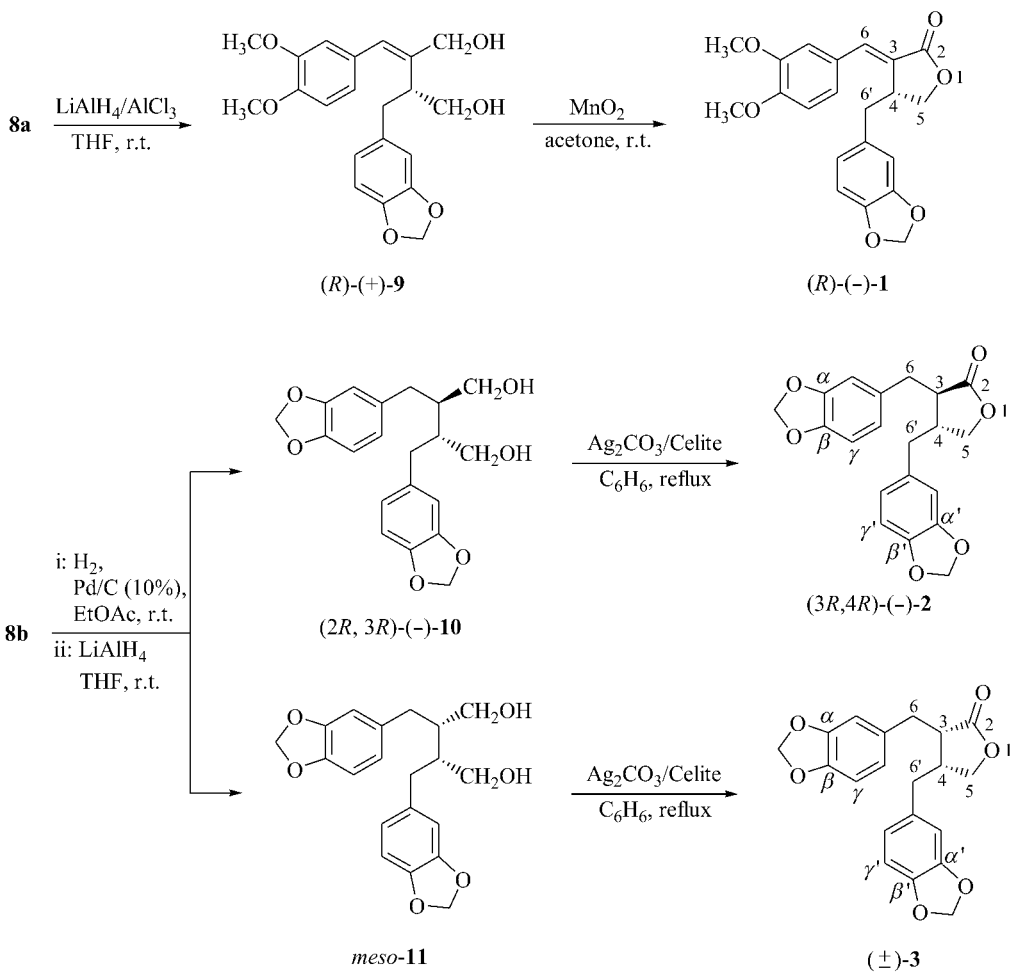



**4a, 4b** **5a, 5b** **6a, 6b**

(*R*)-(−)-**7a, 7b** (*R*)-(−)-**8a, 8b**

**a:** $R^1 = R^2 = OCH_3$; $R^3 = R^4 = CH_3$
**b:** $R^1, R^2 = OCH_2O$; $R^3 = R^4 = C_2H_5$

**Scheme 2**




(*R*)-(+)-**9** (*R*)-(−)-**1**

(2*R*, 3*R*)-(−)-**10** (3*R*,4*R*)-(−)-**2**

*meso*-**11** (±)-**3**

EtOAc), followed by reduction using $LiAlH_4$ in THF produced a readily separable mixture (approximate 1∶1, HPLC) of *threo*-diol **10** and *erythro*-diol **11**. Subjecting the diol **10** to $Ag_2CO_3$/Celite oxidation afforded (−)-hinokinin (**2**) in 92% yield.[10] Similarly, oxidation of the diol **11** with $Ag_2CO_3$/Celite produced (±)-isohinokinin (**3**) in 94% yield.[11] To the best of our knowledge, (*R*)-(−)-kaerophyllin (**1**) was synthesized for the first time. All the spectral data of natural products-(−)-kaerophyllin (**1**),[1] (−)-hinokinin (**2**)[2] and (±)-isohinokinin (**3**)[8] were in agreement with those reported in the literatures.

In conclusion, a rapid and stereoselective route to unsaturated and saturated dibenzylbutyrolatone-lignans was given. The yields were good and the reaction can be performed in molar scales.

## References and notes


1 Mikaya, G. A.; Turabrlidze, D. G.; Kemertelidze, E. P.; Wulfson, N. S. *Planta Medica* **1981**, *43*, 378.

2 Wenkert, E.; Gottlieb, H. E.; Gottlieb, O. R.; Pereira, M. O. S.; Formiga, M. D. *Phytochemistry* **1976**, *15*, 1547.

3 MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207.

4 Chang, S.-T.; Wang, D. S.-Y.; Wu, C.-L.; Shiah, S.-G.; Kuo, Y.-H.; Chang, C.-J. *Phytochemistry* **2000**, *55*, 227.

5 Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 4340.

6 Ghosal, S.; Banerjee, S. *J. Indian Chem. Soc.* **1978**, *LV*, 1201.

7 Kise, N.; Tokioka, K.; Aoyama, Y.; Matsumura, Y. *J. Org. Chem.* **1995**, *60*, 1100.

8 Lu, X.-Y.; Zhu, G.-X. *Synlett* **1993**, *1*, 68.

9 (*R*)-(−)-Kaerophyllin (**1**): White crystals, m.p. 146—147 ℃, $[\alpha]_D^{20}$ − 67.7 (*c* 1.2, $CHCl_3$); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$: 2.61 (dd, *J* = 10.4, 14.4 Hz, 1H, H-6′a), 3.04 (dd, *J* = 4.2 Hz, 14.4 Hz, 1H, H-6′b), 3.75—3.92 (m, 1H, H-4), 3.92 (s, 3H, $OCH_3$), 3.95 (s, 3H, $OCH_3$), 4.27 (d, *J* = 4.0 Hz, 2H, 2 × H-5), 5.94 (s, 2H, $OCH_2O$), 6.61—7.25 (m, 6H, ArH), 7.54 (d, *J* = 1.8 Hz, 1H, H-6); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$: 37.4 (C-6′), 39.6 (C-4), 55.9 (2 × $OCH_3$), 69.4 (C-5), 101.1 ($OCH_2O$), 108.4, 109.0, 111.2, 112.9, 121.9, 123.5, 125.6, 126.8, 131.4 (C-3), 137.4 (C-6), 146.5, 147.9, 149.0, 150.6, 172.6 (C-2); IR (KBr) $\nu$: 2913, 1745, 1644, 1596, 1515, 1249, 1185, 1035, 927, 807 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 368 ($M^+$, 9), 306 (0.3), 233 (69), 135 (100).

10 (3*R*,4*R*)-(−)-Hinokinin (**2**): White crystals, m.p. 63—64 ℃, $[\alpha]_D^{20}$ − 34.2 (*c* 1.3, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 2.42—2.60 (m, 4H, $ArCH_2$, H-3, H-4), 2.83 (dd, *J* = 7.2, 14.1 Hz, 1H, ArCH), 2.98 (dd, *J* = 4.5, 14.1 Hz, 1H, ArCH), 3.86 (dd, *J* = 7.2, 9.3 Hz, 1H, H-5a), 4.13 (dd, *J* = 6.9, 9.3 Hz, 1H, H-5b), 5.93 (s, 2H, $OCH_2O$), 5.94 (s, 2H, $OCH_2O$), 6.50—6.75 (m, 6H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 34.7 (C-6′), 38.3 (C-6), 41.2 (C-4), 46.4 (C-3), 71.1 (C-5), 101.0 (2 × $OCH_2O$), 108.2, 108.3, 108.7, 109.3, 121.5, 122.2, 131.2, 131.5, 146.2, 146.4, 147.8 (C-α, C-α′), 178.4 (C-2); IR (KBr) $\nu$: 2916, 1767, 1494, 1430, 1247, 1037, 928 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 354 ($M^+$, 14), 218 (4), 192 (3), 135 (100).

11 (±)-Isohinokinin (**3**): White crystals, m.p. 115—116 ℃; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 2.29 (t, *J* = 13.5 Hz, 1H, H-6′a), 2.60—2.68 (m, 1H, H-4), 2.73 (dd, *J* = 10.5, 14.7 Hz, 1H, H-6a), 2.88 (dd, *J* = 3.0, 13.5 Hz, 1H, H-6′b), 3.00—3.08 (m, 1H, H-3), 3.22 (dd, *J* = 4.2, 14.7 Hz, 1H, H-6b), 3.98—4.07 (m, 2H, 2 × H-5), 5.92 (s, 2H, $OCH_2O$), 5.96 (s, 2H, $OCH_2O$), 6.51—6.54 (m, 2H, ArH), 6.71—6.81 (m, 4H, ArH); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 30.5 (C-6′), 32.5 (C-6), 39.9 (C-4), 45.2 (C-3), 69.3 (C-5), 101.0 (2 × $OCH_2O$), 108.4 (C-γ, C-γ′), 108.6, 109.0, 121.2, 121.9, 132.0, 132.1, 146.2 (C-β, C-β′), 147.9 (C-α, C-α′), 177.8 (C-2); IR (KBr) $\nu$: 2902, 1771, 1490, 1443, 1248, 1038, 927, 809 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 354 ($M^+$, 12), 218 (7), 192 (5), 135 (100).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