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A new shortcut synthesis route for (±)raphidecursinol

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Abstract

The new shortcut synthesis route of (±)raphidecursinol **1**, a racemic 8,4′-oxyneolignan compound, can be more easily achieved by the synthesis route, starting from readily available inexpensive 3,4,5-trimethoxy-benzaldehyde and 1,2,3-trihydroxybenzene. All structures were confirmed by ^{1}H NMR, IR and MS.

Keywords: 8,4′-Oxyneolignan; Raphidecursinol; Racemic compound

Raphidecursinol, isolated from myristicaceae and other primitive plant families in neotropical regions, is a natural 8,4′-oxyneolignan compound, which displays interesting and varied biological properties spanning from anti-malarial [1–3] to anti-fungal [4], anti-leishmanial [5], anti-oxidant [6], and anti-schistosomial [7] activities. However, obtaining supplies from nature is an arduous task due to the scarce quantity of isolable compounds and the fact that most of the isolated neolignans reported present themselves as racemic mixtures [8,9]. Therefore, it has attracted continued interest to develop a convenient total synthesis route to obtain the natural 8,4′-oxyneolignan compound and more optical derivates.

Lee and Ley [10] reported the preparation of the target compound **1**. However, this approach was not economical because it included the application of costly enzyme and polymer catalyst. Recently, Claudio et al. [11] have used (S)-methyl lactate as start material to synthesize **1**. But this route was also too complicated and the ee% was poor. Because of favorable biological activity of **1**, we want to search for a potential total synthesis route and modify its structure to discover more potential derivatives. Herein, we have reported a new efficient shortcut synthesis route for **1**.

As shown in Scheme 1, we believed that the target compound **1** could be derived from the activated methanesulfonate **2** or **3** and phenol **4**. If successful, this approach would enable us to introduce different substituents as hydroxyl derivatives at a late stage of the synthesis and thereby facilitate the preparation of this series of analogues. The synthesis of the two parts has been shown respectively in Schemes 2 and 3.

The synthesis method of new compound **2** has been shown in Scheme 2. Knoevenagel reaction of 3,4,5-trimethoxybenzaldehyde **5** with malonic acid led to acid **6**. In the reduction from **6** to **7**, we first tried to get **7** by esterifying **6** followed by reduction with $LiAlH_4$ [12]. However, it failed to get the target compound. Instead of **7**, unsatisfied saturated compound 3-(3,4,5-trimethoxyphenyl)-propan-1-ol was unexpectedly generated. Then acid **6**

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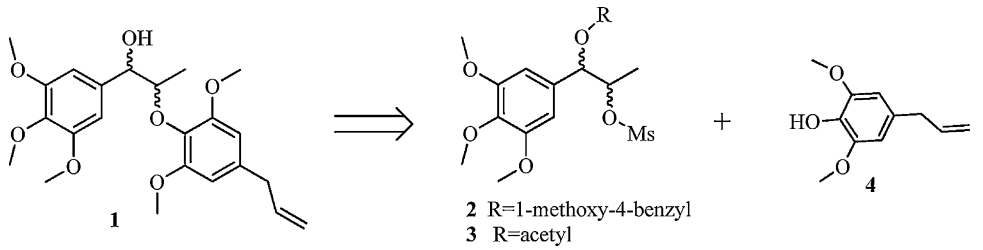
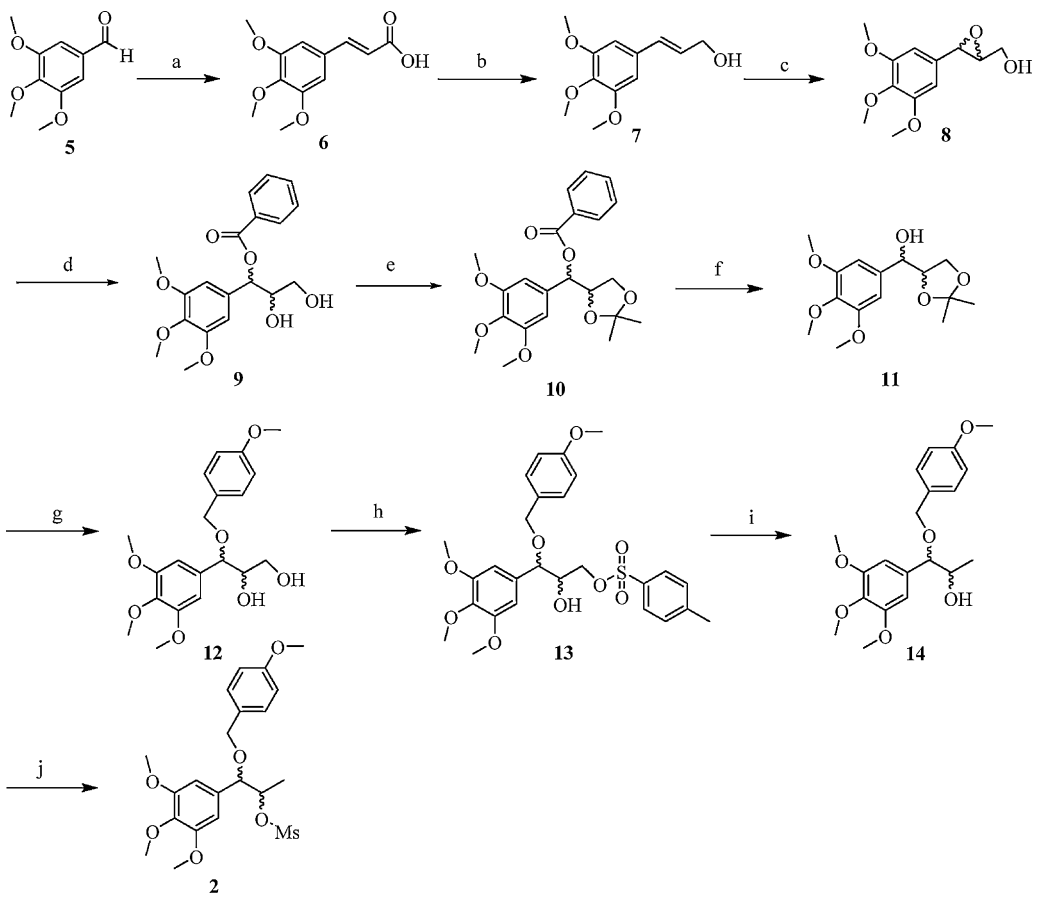
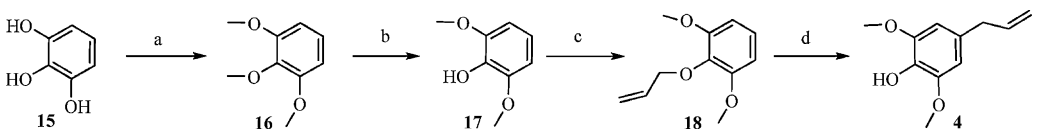


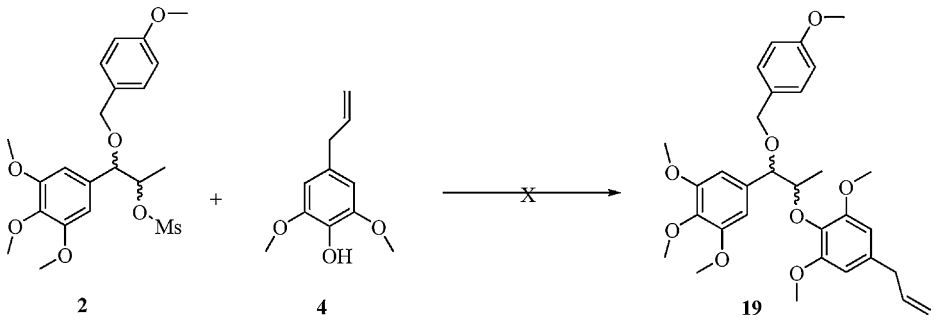
Scheme 1. The retrosynthesis route of the compound **1**.



Scheme 2. The synthetic route of key compound **2**. Condition and regent: (a) pyridine, piperidine, malonic acid, 120 °C, 6 h, 80%; (b) i: $SOCl_2$, CH_2Cl_2, r.t., 12 h; ii: $NaBH_4$, THF, CH_3OH, 4 h, 86% in two steps; (c) $VO(acac)_2$, TBHP, CH_2Cl_2, r.t., 2 h, 75%; (d) benzoic acid, titanium tetraisopropoxide, CH_2Cl_2, 0 °C, 3 h, 85%; (e) 2,2-dimethoxypropane, pyridine, TsOH, CH_3CN, 40 °C, 3 h, 90%; (f) K_2CO_3, MeOH, H_2O, r.t., 4 h, 95%; (g) i: 4-methoxybenzylchloride, NaH, DMF, r.t., 2 h; ii: THF, 2 mol/L HCl, r.t., 3 h, 70% in two steps; (h) TsCl, pyridine, 0 °C, 18 h, 71%; (i) $LiAlH_4$, THF, 4 h, r.t., 81%; (j) Et_3N, CH_2Cl_2, MsCl, 1 h, r.t., 80%.



Scheme 3. The synthetic route of key compound **4**. Condition and regent: (a) CH_3I, 6 h, 80%; (b) $AlCl_3$, CH_2Cl_2, r.t., 12 h, 82%; (c) 3-bromopropene K_2CO_3, CH_2Cl_2, r.t., 2 h, 75%; (d) 170 °C, 20 h, 85%.



Scheme 4. The synthesis strategy of the compound **19**.

was chlorinated with $SOCl_2$ to give the activated chloride derivative, which was easily reduced to give alcohol **7** by the method reported by Kang and Lee [13]. Alcohol **7** was oxidized under the effectiveness of $VO(acac)_2$ catalyst to give the racemic epoxy derivative **8** [14]. Besides, the optical epoxide **8** could also be obtained under the standard sharpless condition. On the whole, this method can efficiently get more analogues and optical derivatives. Compound **8** was substituted regioselectivity by benzoic acid under the effectiveness of titanium tetraisopropoxide by ring cleavage to obtain diol **9**. Diol **9** was protected by 2,2-dimethoxypropane to get **10**, followed by hydrolysis to get alcohol **11**. **11** was substituted by 4-methoxybenzylchloride under the effectiveness of NaH, then deprotected isopropylidene group to obtain diol **12**. **12** was esterified regioselectivity with TsCl in pyridine to get alcohol **13**, followed by reduction with $LiAlH_4$ to give alcohol **14**. Secondary alcohol **14** can be converted with MsCl to obtain key intermediate **2** by methylsulfonylation.

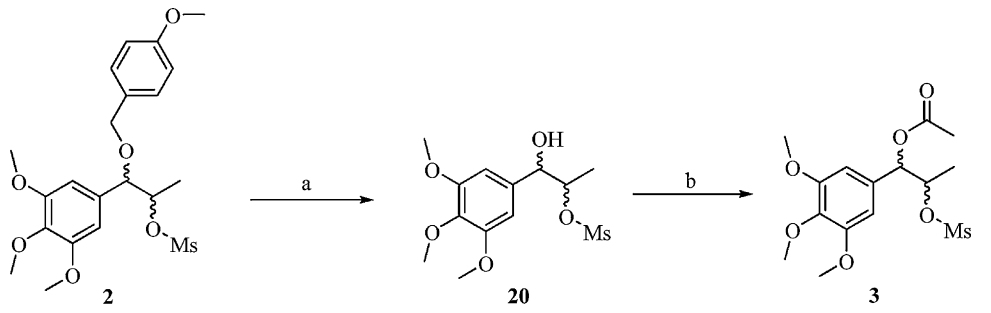
The synthetic route of compound **4** has been shown in Scheme 3. By modifying the method reported by Jing and Wang [15], the treatment of 1,2,3-trihydroxybenzene **15** with CH_3I afforded the corresponding trimethylated product **16**, which was regioselectively demethylated by $AlCl_3$ to get dimethylated product **17**. **17** was first converted to give **18** by reaction with 3-bromopropene, then followed by rearrangement at 170 °C to get the key intermediate **4**.

The etherification reaction between **2** and **4** has been investigated. We have probed different etherification methods in the experiment. Cs_2CO_3, K_2CO_3, etc., have been employed to promote the etherification. Unfortunately, as shown in Scheme 4, all tested conditions failed to give any desired product **19**, owing to the stereospecific blockade of 1-methoxy-4- benzyl of **2** when effected by attack of 4-allyl-2,6-dimethoxyphenol **4**.

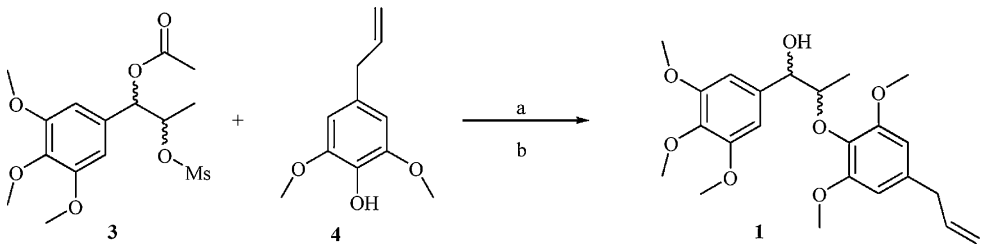
Therefore, the stepwise transformation of 1-methoxy-4-benzyl compound **2** into the known acetyl compound **3** [11] was investigated alternatively by the deprotection under the effectiveness of DDQ, then esterification with AcCl, which is outlined in Scheme 5.

With key intermediates **3** and **4** in hand [16], we can easily get the target compound **1** by the method reported by Claudio et al. [11], which is outlined in Scheme 6.

In summary, we have provided a new shortcut synthesis route, starting from readily available and inexpensive 3,4,5-trimethoxybenzaldehyde and 1,2,3-trihydroxybenzene, for the preparation of (±)raphidecursinol. The studies for optical compounds and synthesis of derivatives are underway.



Scheme 5. The synthetic route of key point compound **3**. Condition and regent: (a) DDQ, CH_2Cl_2, r.t., 18 h, 90%; (b) AcCl, CH_2Cl_2, Et_3N, DMAP, r.t., 6 h, 83%.



Scheme 6. The synthetic route of target compound **1**. Condition and regent: (a) Cs_2CO_3, 18-crown-6, DMF, sonication, then MW (200 W, 2 bar, 120 °C, 10 min), 72%; (b) NaOMe, MeOH, 99%.

Acknowledgment

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[16] All new compounds were characterized by elemental analysis, IR, MS and ^{1}H NMR spectra data. Selected analytical data: **2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, 2H, J = 6.4, 2.0 Hz), 6.88 (dd, 2H, J = 6.4, 2.0 Hz), 6.54 (s, 2H), 4.79 (m, 1H) 4.43 (d, 1H, J = 11.2 Hz), 4.21–4.27 (m, 2H), 3.87 (s, 9H), 3.81 (s, 3H), 2.92 (s, 3H), 1.06 (dd, 2H, J = 6.4, 57.2 Hz); MS (EI): 441.15 (M^+) IR (KBr/cm^{-1}): 3415, 2931, 2873, 1612, 1511, 1350, 1245, 1120, 1085, 987, 819, 782, 531, 507; (Found: C, 57.31; H, 6.38. Calcd. for $C_{20}H_{18}O_8$ C, 57.26; H, 6.41%). **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55(d, 2H, J = 2 Hz), 5.70 (d, 1H, J = 7.2 Hz), 4.99 (qd, 1H, J = 6.2, 4.8 Hz), 3.87 (s, 6H), 3.83 (s, 3H), 2.91 (s, 3H), 2.16 (s, 3H), 1.06 (dd, 3H, J = 6.4, 57.2 Hz); MS(EI): 363.10 (M^+) IR (KBr/cm^{-1}): 2950, 2870, 1750, 1609, 1511, 1487, 1411, 1351, 1304, 1271, 1250, 1220, 1130, 1063, 987, 819, 803, 760, 713, 531, 507. (Found: C, 49.66; H, 6.25. Calcd. for $C_{15}H_{22}O_8S$ C, 49.71; H, 6.12%); **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (s, 2H), 5.93 (m, 1H), 5.38 (s, 1H), 5.05–5.11 (m, 2H), 3.88 (s, 3H), 3.32 (d, 2H, J = 6.8 Hz), 2.16 (s, 3H), 1.06 (dd, 3H, J = 6.4, 57.2 Hz); MS (EI):195.07 (M^+) IR (KBr/cm^{-1}): 3550, 2980, 2890, 1610, 1510, 1463, 1412, 1351, 1220, 1100, 921, 850, 855 (Found: C, 68.08; H, 7.23. Calcd. for $C_{11}H_{14}O_3$ C, 68.02; H, 7.27%).