Concise and efficient total synthesis of oxyphyllacinol, yakuchione-A and yakuchione-B

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ABSTRACT
A concise and efficient method for the large-scale total synthesis of oxyphyllacinol (1) has been achieved in six steps with an overall yield of 46%. Simultaneously, yakuchione-A (11) was obtained in a satisfactory yield (52%) during the process. By employing a Weinreb amide (6) as the key masonry block, yakuchione-B (13) was also constructed in a great overall yield (56%) and high purity. To overcome the challenges regarding the practical scale, high purity, and reproducibility, the synthetic route that was processed takes advantage of available materials, conventional reactions, and convenient purification methods without using column chromatography.

GRAPHICAL ABSTRACT

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Oxyphyllacinol; large-scale synthesis; yakuchione-A; yakuchione-B

Introduction
Zingiberaceae (Yi-zhi in Chinese), a Chinese traditional medicine, has widely been used for the treatment of various diseases such as malaria,[1] flatulence,[2] dyspepsia,[3] polyuria, and gastralgia.[4] Previous studies have revealed that diarylheptanoids, including oxyphyllacinol (1), yakuchione-A (11), and yakuchione-B (13) (Fig. 1), act as a class of active constituents in Zingiberaceae that play an important role in several biological activities.[5]
Among these diarylheptanoids, oxyphyllacinol (1), which contains a phenylpropanol skeleton, exhibits significant inhibition of nitric oxide (NO) production against inflammatory disease.[6] Yakuchinone-A (11) is very similar to oxyphyllacinol (1) in terms of structure except that the alcohol group at position 3 is replaced by a ketone carbonyl group. Previous studies have demonstrated that it displays several pharmacological properties such as anti-inflammatory,[7] anti-Alzheimer’s,[8] antioxidant[9] and tumor preventing properties,[7] and the inhibition of acyl-CoA.[10] In addition, yakuchinone-B (13) has an unique structure with a conjugated moiety of α, β-unsaturated carbonyl in the linker, and it overall exerts stronger biological activities than yakuchinone-A (11) does,[11] which may be attributed to the enone group. However, despite having a wide range of biological activities, these three compounds are rarely available on the market in large quantities, thus hindering their further development and utilization in the pharmaceutical and nutraceutical industries. In the view of that, it is of practical importance to develop a concise and efficient synthetic method to achieve large-scale preparation of these three diarylheptanoids.

To date, several synthetic methods for yakuchinone-A (11) and yakuchinone-B (13) have been reported. As shown in Scheme 1, Oh et al. using coniferaldehyde (14) as the raw material can construct yakuchinone-B (13) through four steps.[12] Unfortunately, this method is not suitable for large-scale synthesis due to the usage of an expensive material (14). Additionally, the addition of Grignard reagent to compound 15 need to be performed at −78 °C, which may pose a challenge to the production equipment, as well as the fact that column chromatography is essential for all the intermediates in this process.

The first total synthesis of yakuchinone-A (11) was reported by Itokawa et al. (Scheme 2) in 1981.[13] Itokawa used Me₂Cd as a methylation reagent to construct compound 20, but nevertheless, the high cost of Me₂Cd severely limits its large-scale application in the preparation of 20. Furthermore, as the previous study for the synthesis of [6]-Paradol reported[14] (Scheme 3), when the α, β-unsaturated ketone is hydrogenated with H₂ in the presence of Pd/C, an equivalent amount of oxyphyllacinol (1) might be produced along with yakuchinone-A (11).

To achieve the selective reduction of the ketone carbonyl groups in α, β-unsaturated ketone fragment, Nishiyama et al. have reported an active reducing species by using selenium with carbon monoxide and water.[15] (Scheme 2). However, this method requires...
the use of high-pressure equipment and highly toxic CO, which would severely limit its application in large-scale production.

To overcome the drawbacks of the reported methods, we intend to develop a concise, efficient, cost-effective, and reproducible synthetic strategy for the simultaneous preparation of oxyphyllacinol (1), yakuchinone-A (11) and yakuchinone-B (13). Given a general phenomenon that many natural products share a similar parent structure, they
have some commonality in the design of synthetic routes. To the best of our knowledge, [6]-Paradol, one of the bioactive components isolated from ginger, has a similar structure to diarylheptanoids in terms of propiophenone. It is worth mentioning that we have successfully synthesized [6]-Paradol by introducing weinb amide in our previous work,[14] and as a continuation of this work, we intend to develop an efficient synthetic strategy suitable for industrial production for oxyphyllacinol (1), yakuchinone-A (11) and yakuchinone-B (13), simultaneously, that will give a great potential value in the pharmaceutical and nutraceutical fields.

Results and discussion

The retrosyntheses for oxyphyllacinol (1), yakuchinone-A (11) and yakuchinone-B (13) are shown in Fig. 2. We anticipated that oxyphyllacinol (1) could be transformed from yakuchinone-A (11), which itself would be formed through a reduction reaction of 6 followed by a deprotection reaction and a Grignard reaction. Compound 6, the key intermediate, could be obtained via Wittig-horner reaction from 3. This compound is to be generated, according to the method,[16] by using commercially available vanillin (2) as the starting material. Meanwhile, with compound 6 in hand, it was expected that yakuchione-B (13) could also be prepared through the method for the synthesis of yakuchione-A (11).

Our synthesis commenced with known intermediate 3, which was obtained through a reported method[16] from commercially available vanillin (2). Treatment of 3 with Wittig reagent diethyl (2-(methoxy(methyl)amino)-2-oxoethyl)phosphonate (5), which was prepared through the reported method,[14] afforded Weinreb amide (6) in 96% yield (Scheme 4).

Subsequently, in the presence of Pd/C and H2, 6 was subjected to hydrogenation to afford compound 7 in 98% yield. Then 7 underwent desilylation with TBAF to give 8 in excellent yield (98%). With compound 8 in hand, we initially treated 4-Phenylbutanol (9) with PBr3 to prepare 10.[17] Following then, it was treated with magnesium and a catalytic amount of I2 to prepare Grignard reagent. 2.7 equivalent of Grignard reagent was condensed with 8 at room temperature to give a crude product of
compound 11, which was distilled under vacuum (90 Torr) at 52 – 54 °C to give pure yakuchinone-A (11) in 72% yield. Treating 11 with 2 N NaBH₄ in MeOH at room temperature and recrystallized by a mixture of Hexane/petroleum ether (~1:5, -10 °C), the target product 1 was generated in 87% yield (Scheme 5).

The elaboration of compound 6 to yakuchinone-B (13) was achieved involving an initial desilylation of 6 in the presence of TBAF to give 12 in satisfactory yield (95%, Scheme 6). 12 was then converted to yakuchinone-B (13) (77% yield) using Grignard reagent 7 in THF at room temperature and purified by recrystallization (Hexane/petroleum ether, ~3:1, 0 °C).

Conclusion

In summary, a concise and efficient method for simultaneous large-scale synthesis of oxyphyllacinol (1), yakuchione-A (11), and yakuchione-B (13) has been achieved in this study. To overcome the challenges regarding the high yield, high purity and reproducibility, all the synthetic processed highlights available materials, conventional reactions, and convenient purification method without involving column.

Experimental

All reagents were purchased from commercial suppliers and used without further purification unless stated otherwise. ¹H-NMR and ¹³C-NMR spectra were recorded on Bruker AV 500 spectrometer using DMSO-d₆ or CDCl₃ as the solvent. Chemical shifts were given in Hz and coupling constants were expressed as δ values in ppm. The following multiplicity abbreviations were used: (s) singlet, (d) doublet, (t) triplet, (q)
quartet, (m) multiplet, (br) broad, (dd) double doublet, (dt) double triplet. Mass spectra (MS) were collected on Agilent 1100 spectrometer. Flash column chromatography was done using silica gel (100–200 mesh). Thin-layer chromatography (TLC) was performed using HSGF 254 nm precoated plates obtained from Qindao Haiyang Chemical Technology Co., Ltd.

The preparation of compounds 3–8, compound 10, and compound 12 are described in the Supporting Information, according to the reported methods.

Yakuchinone-A (11)

To a solution of I2 (2 g) and magnesium (24 g, 1.0 mol, 2.7 equiv) in dry THF was added dropwise 10 (213 g, 1.0 mol, 2.7 equiv) at 40°C under Ar atmosphere. After stirred for 1 h, the reaction mixture was cooled to 0°C, and a solution of 8 (1 M THF, 370 mL, 0.37 mol, 1.0 equiv) was added dropwise. Subsequently, the mixture was warmed to room temperature along with being stirred for a further 3 h. Completion of the reaction (monitored by TLC), the solvent was removed in vacuo to give yellow residue, which was then diluted with EtOAc. The resulting organic layer was washed with brine, concentrated under reduced pressure to give the crude product, which was distilled under vacuum (90 Torr) at 52–54°C to give pure yakuchinone-A (11) (83 g, 72%) as gray oil. 1H NMR (500 MHz, CDCl3) δ 7.22–7.25 (m, 2H, Ar-H), 7.11–7.15 (m, 3H, Ar-H), 6.79 (d, J = 8.0 Hz, 1H, Ar-H), 6.64 (s, 1H, Ar-H), 6.62 (d, J = 8.0 Hz, 1H, Ar-H), 5.47 (s, 1H, OH), 3.82 (s, 3H, OCH3), 2.79 (t, J = 7.4 Hz, 2H, CH2), 2.64 (t, J = 7.4 Hz, 2H, CH2), 2.57 (t, J = 7.0 Hz, 2H, CH2), 2.36 (t, J = 6.4 Hz, 2H, CH2), 1.56–1.59 (m, 4H, CH2CH2); 13C NMR (125 MHz, CDCl3) δ 210.18 (CHO), 146.42, 143.94, 142.16, 133.06, 128.35, 128.30, 125.75, 120.78, 114.35, 111.11, 55.88, 44.60, 42.90, 35.71, 30.94, 29.55, 23.41; HR-MS (ESI) calcd for C20H23O3 [M-H] – 311.4090, found 311.4068. All the above data are consistent with those reported in the literature.[13]

Oxyphyllacinol (1)

A solution of 11 (40 g, 0.13 mol, 1.0 equiv) in MeOH was added NaBH4 (10 g, 0.26 mol, 2.0 equiv) portion-wise at 0°C. Then the reaction temperature was heated to room temperature along with being stirred for 2 h. After completion of the reaction (monitored by TLC), excess NaBH4 was quenched with water and the solvent was removed under reduced pressure. EtOAc and water were added to the residue. The organic layer was separated, washed with brine, dried over anhydrous Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallization (Hexane/petroleum ether, ~1:5, −10°C) to afford oxyphyllacinol (1) (71 g, 87%) as white waxy solid at 0°C. 1H NMR (500 MHz, CDCl3) δ 7.24 (d, J = 7.9 Hz, 2H, Ar-H), 7.14 (d,
$J = 7.9 \text{ Hz, } 3\text{H, Ar-H}, 6.81 \text{ (d, } J = 7.8 \text{ Hz, } 1\text{H, Ar-H}), 6.67 \text{ (s, } 1\text{H, A-H), 6.66 (d, } J = 7.8 \text{ Hz, } 1\text{H, Ar-H), 3.85 (s, } 3\text{H, OCH}_3, 3.63-3.57 \text{ (m, } 1\text{H, CHOH), 2.66-2.72 \text{ (m, } 1\text{H, ArCH}_2\text{CH}_2\text{CHOH), 2.59 (t, } J = 7.5 \text{ Hz, } 2\text{H, CH}_2, 2.58-2.54 \text{ (m, } 1\text{H, ArCH}_2\text{CH}_2\text{CHOH), 1.76-1.65 \text{ (m, } 2\text{H, CH}_2, 1.64-1.53 \text{ (m, } 2\text{H, CH}_2, 1.54-1.41 \text{ (m, } 3\text{H, CH}_2 \text{ and } \text{CH}_2\text{CH}_2\text{CHOH), 1.39-1.33 \text{ (m, } 1\text{H, } \text{CH}_2\text{CH}_2\text{CHOH); } ^{13}\text{C NMR (125 MHz, CDCl}_3 \text{ } \delta = 146.44, 143.74, 142.52, 134.05, 128.37, 128.27, 125.67, 120.91, 114.29, 111.03, 71.30, 55.88, 39.35, 37.45, 35.88, 31.75, 31.44, 25.26; HR-MS (ESI) calcd for } \text{C}_{20}\text{H}_{25}\text{O}_3 [M-H]^-= 313.4250, \text{ found } 313.4226. \text{ All the above data are consistent with those in the reported literature.}^{[18]}

**Yakuchinone-B (13)**

Compound 12 (70 g, 0.29 mol, 1.0 equiv) was condensed with 10 (169 g, 0.8 mol, 2.7 equiv) following the procedure of yakuchinone-A (11). The crude product was purified by recrystallization (Hexane/petroleum ether, ~3:1, 0 °C) to afford yakuchinone-B (13) (69 g, 77%) as yellow solid. m.p. 74–75 °C; $^1\text{H NMR (400 MHz, CDCl}_3 \text{ } \delta = 7.47 \text{ (d, } J = 16.0 \text{ Hz, } 1\text{H, PhCH=CH), 7.26 \text{ (d, } J = 6.1 \text{ Hz, } 2\text{H, Ar-H}, 7.18 \text{ (d, } J = 6.6 \text{ Hz, } 3\text{H, Ar-H), 7.09 \text{ (d, } J = 7.6 \text{ Hz, } 1\text{H, Ar-H), 7.04 \text{ (s, } 1\text{H, Ar-H), 6.92 \text{ (d, } J = 7.6 \text{ Hz, } 1\text{H, Ar-H), 6.58 \text{ (d, } J = 16.0 \text{ Hz, } 1\text{H, PhCH=CH), 5.92 \text{ (s, } 1\text{H, OH), 3.93 \text{ (s, } 3\text{H, OCH}_3), 2.71-2.62 \text{ (m, } 4\text{H, CH}_2\text{CH}_2, 1.77-1.65 \text{ (m, } 4\text{H, CH}_2\text{CH}_2; ^{13}\text{C NMR (100 MHz, CDCl}_3 \text{ } \delta = 200.25 \text{ (C = O), 148.12, 146.78, 142.60, 142.17, 128.27, 127.05, 125.70, 124.03, 123.34, 114.76, 109.35, 56.02, 40.26, 35.73, 31.05, 24.04; HR-MS (ESI) calcd for } \text{C}_{20}\text{H}_{21}\text{O}_3 [M-H]^-= 309.3929, \text{ found } 309.3941. \text{ All the above data are consistent with those in the reported literature.}^{[12]}

**Supporting information**

Supporting Information: $^1\text{H NMR and } ^{13}\text{C NMR spectra of target compounds and interbodies. This material can be found via the "Supplementary Content" section of this article's webpage.**

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