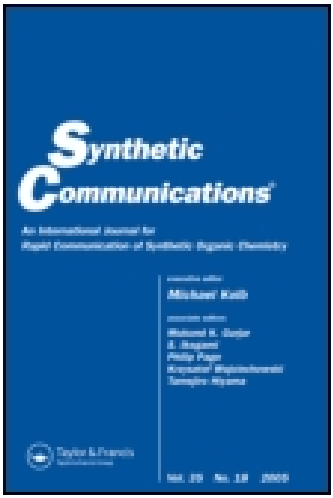

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A Convenient Strategy for the Total Synthesis of Pisiferic Acid Type Diterpenes

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A Convenient Strategy for the Total Synthesis of Pisiferic Acid Type Diterpenes

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Abstract: A practical method for the total synthesis of pisiferic acid type diterpenoids is described. This involves Robinson annulation of the keto ester for the key intermediate.

Keywords: Diterpenoid, pisiferic acid, robinson annulation, total synthesis

INTRODUCTION

(+)-Pisiferic acid **1** (Scheme 1) is a kind of C-aromatic tricyclic diterpene acids, which was first isolated from the leaves and twigs of *Chamacecpyparis pisifers* Endle in 1978.[1] Since then, the isolation of other structural related compounds, such as (+)-pisiferial **2**,[2] (+)-pisiferol **3**,[3] (+)-*O*-methyl pisiferic acid **4**,[2] (+)-*O*-methyl pisiferate **5**,[2] and (+)-blephaein **6**,[4] were reported. These natural products have many important biological activities, such as antimicrobial activity[5] and regulating mite growth activity.[6] This triggered many interests for their synthesis.

Pisiferic acids are different from the other C-aromatic tricycle diterpenoids because they have a unique oxidized angular group instead of a methyl angular group. In the case of a methyl angular group, the tricycle framework can be established easily using cyclization catalyzed by Lewis acids, and their total syntheses have been fully studied.[7] However, the

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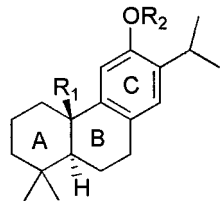
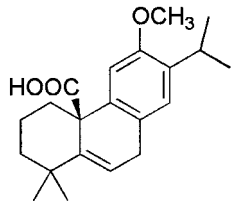


1. R_1=COOH R_2=H
2. R_1=CHO R_2=H
3. R_1=CH_2OH R_2=H
4. R_1=COOH R_2=CH_3
5. R_1=$COOCH_3$ R_2=H



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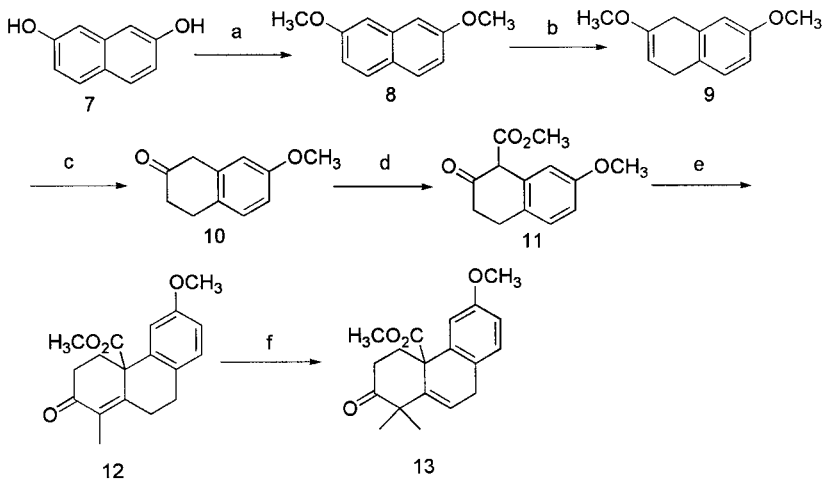
Scheme 1.

unique oxidized angular group of pisiferic acids makes their total synthesis difficult. Mori et al. reported a route for the total synthesis of (±)-Pisiferol. It started from a Wieland-Miescher ketone[8] and followed by mutisteps construction of the aromatic C-ring. Similar approaches have also been published.[9–11] Another strategy was reported by Mukherjee et al., where aryl participated intramolecular cyclization of the diazomethyl ketone was applied.[12,13] All the reported methods have some limitations, such as tedious synthetic procedures, difficulty in practice, low overall yield, and starting materials that are commercially unavailable.

We aimed to develop a new methodology for the synthesis of pisiferic acids and their analogues, which would be feasible in practical and useful for elucidating their structure and activity relationship. The method involved the initial synthesis of a key intermediate. The catalytic hydrogenation of the intermediate would generate the *trans*-stereochemistry at the A/B ring junction[14] and can be applied for further synthesis. Here, we reported a practical approach for the synthesis of the key intermediate (Scheme 2, compound **13**) using Robinson annulation.

RESULTS AND DISSCUSSION

The alkoxynaphthalene **8** (scheme 2) was prepared from the commercially available 2,7-dihydroxynaphalene **7** in 97% yield.[15,16] The dihydro enol ether **9** was synthesized by the selective Birch reduction of **8**.[17] The selectivity in the reduction was due to a highly resonance stabilized benzene structure of **9**, which inhibited its further reduction. The reaction conditions have been optimized, showing that 2.6 equivalent of metallic sodium produced a good yield. Acid hydrolysis of **9** yielded the 2-tetralon **10** in 80% overall yield.



Scheme 2. Reagents and Conditions: (a) 10% NaOH, Me_2SO_4; (b) Na, NH_3(l); (c) 3 N HCl, Acetone, rt, 3 h; (d) NaH, $CO(OCH_3)_2$, Benzene, reflux; (e) CH_3ONa, CH_3OH, EVK; (f) t-BuOK, t-BuOH, CH_3I, 50–60°C.

In order to synthesize the tricyclic intermediate **13**, it is critical to introduce a carboxylic group at the angular position. Our initial attempt was to carboxymethylate the 2-tetralone **10** using the classic enamine method.[18] It started with conversion of **10** into the corresponding enamine by the procedure of Stork with tetrahydropyrrole. A subsequent reaction of the enamine with methyl chloroformate yielded only 15% keto ester **11**. An improved method has been explored later using a similar approach for the high-yield carboxymethylation of 6-methyl-5- heptene-2-one.[19] The keto ester **11** has been prepared in a quantitative yield by the reaction of **10** with dimethyl carbonate and excess of sodium hydride in benzene. Worthy to note, most of **11** was in its enolic form as determined by ^{1}H NMR.

For the further construction of the A-cycle, **11** was reacted with ethyl vinyl ketone (EVK) to yield the tricyclic nucleus **12** using Robinson annulation.[20] Under the classic refluxing condition,[20] the reactants were too complex to isolate **12**. However, when the reaction was stirred overnight at room temperature using sodium methoxy as the base, a high yield of **12** was been achieved directly, which did not need further base-catalyzed intramolecular aldol cyclization. The subsequent reaction of **12** with ^{t}BuOK and CH_3I at 50–60°C for 5 h gave the key intermediate **13** in 63% yield. Its structure has been determined by various NMR spectrums.

In summary, a practical route for the total synthesis of pisiferic acid type diterpenoids has been developed. It started with a commercially available reagent and used Robinson annulation of the keto ester in one-step reaction for its key intermediate. Works are continuing in our lab for the total

synthesis and the asymmetric total synthesis of similar natural products and their derivatives.

EXPERIMENTAL

All commercially obtained chemicals were used as received. Tetrahydrofuran (THF) and Benzene were freshly distilled from sodium/benzophenone ketyl. Methanol was dried over Magnesium. ^{t}BuOH was dried over sodium. ^{t}BuOK was purchased from Aldrich Company. Melting points were uncorrected. IR spectra were recorded on an Avatar Nicolet 360 system infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Buker AC-400 MHz spectrometer. Chemical shifts (δ) were given in ppm relative to TMS and coupling constants (J) were given in Hz. ESI mass spectra were acquired using a Bruker Esquire-LC ion trap mass spectrometer in positive ion mode. High-resolution ESI mass spectra were obtained on a Bruker APEX II spectrometer in positive ion mode.

7-Methoxy-2-tetralone 10

To a solution of alkoxynaphthalene **8** (10 g, 5.3 mmol) in anhydrous ethanol (50 mL), liquid ammonia (about 200 mL) was condensed. Metallic sodium (3.1 g, 13.5 mmol) was added in small pieces. After the solution's blue color disappeared, excess ammonium chloride (10 g) was added in portions. The reaction mixture was kept at room temperature until most of the ammonia was evaporated. The residue was poured into water (100 mL), then acidified to pH 5 with 3 N hydrochloric acid and extracted with ether (3 × 100 mL). The combined organic extracts were washed with brine and then dried over sodium sulfate and evaporated. The crude product **9** can be used without further purification.

A solution of **9** in acetone (50 mL) and hydrochloric acid (3N, 10 mL) was refluxed for 30 min under Argon. Acetone was evaporated off and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and evaporated. Purification by vacuum distillation gave **10** (8.2 g, 88.0% yield) as a colorless solid.

IR: 3000, 2947, 1716, 1611, 1504, 1261, 1154, 1038, 813

^{1}H NMR ($CDCl_3$, 300 MHz): 7.14 (d, 1H, J = 8.4 Hz), 6.76 (dd, 1H, J = 2.4 Hz, J = 8.4 Hz), 6.67(d, 1H, J = 2.4 Hz), 3.79(s, 3H), 3.55(s, 2H), 3.00(t, 2H, J = 6.6 Hz), 2.54(t, 2H, J = 6.6 Hz)

ESI-MS(+): 199 $(M + Na)^+$

Methyl 7-Methoxy-2-oxotertralin-1-carboxylate 11

NaH (50%) (2.6 g, 54 mmol) was washed with dry petroleum ether three times (20 mL × 3). After the petroleum ether was decanted, dry benzene (50 mL) and dimethyl carbonate (3.2 mL, 38 mmol) were added. The mixture was heated to reflux. A solution of 7-Methoxy-2-tetralone **10** (3.33 g, 18.9 mmol) in dry benzene (20 mL) was added slowly during 1 h under Argon. The reaction mixture was refluxed for another 2 h and then stirred overnight at room temperature. Acetic acid (10 mL) was added carefully to destroy excess NaH. Then the mixture was poured into ice water (100 mL). The product was extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water, brine, and dried over sodium sulfate. After the solvent was removed under reduced pressure, purification by vacuum column chromatography on silica gel (eluant: petroleum ether/ethyl acetate 20 : 1) gave the **11** (4.40 g) in almost quantitative yield as colorless oil, which solidified in the refrigerator.

IR: 2951, 1640, 1605, 1489, 1447, 1319, 1234, 873

^{1}H NMR ($CDCl_3$, 400 MHz): 13.39 (s, 1H), 7.29 (d, 1H, J = 2.6 Hz), 7.00 (d, 1H, J = 8.2 Hz), 6.59 (dd, 1H, J = 2.6 Hz, J = 8.2 Hz), 3.89 (s, 3H), 3.78 (s, 3H), 2.72 (t, 2H, J = 7.5 Hz), 2.50 (t, 2H, J = 7.5 Hz).

^{13}C NMR ($CDCl_3$): 178.9, 172.3, 158.1, 132.3, 127.5, 125.4, 112.8, 109.1, 99.7, 55.2, 51.6, 29.9, 26.7.

ESI-MS(+): 257 $(M + Na)^+$

6-Methoxy-1-methyl-2-oxo-3,4,9,10-tetrahydro-2H-phenanthrene-4a-carboxylic acid methyl ester 12

To a stirred solution of keto ester **11** (1.807 g, 7.72 mmol) in dry methanol (20 mL), 30% (wt %) sodium methoxide in methanol (432 mg, 8.00 mmol) was added slowly under Argon atmosphere at 0°C. The obtained solution was stirred for another 30 min. The solution turned purple. Ethyl vinyl ketone (EVK) (672 mg, 8.00 mmol) was added to the solution in one portion. The solution was stirred overnight at room temperature. The mixture was acidified to pH 4 with hydrochloric acid (1N). Most of the methanol was evaporated under vacuum, and ether (100 mL) was added. The ether was washed with 5% $NaCO_3$, water, brine, and dried over sodium sulfate. After removal of the solvent under reduce pressure, purification by vacuum column chromatography on silica (eluant: petroleum ether/ethyl acetate 8 : 1) gave the product **12** (1.12 g) in 75.5% yield (based on recovered keto ester 650 mg) as colorless crystalline.

m.p.: 97–98°C

IR: 3005, 2950, 1718, 1664, 1610, 1236, 1163, 865

^{1}H NMR ($CDCl_3$, 400 MHz): 7.03 (d, 1H, J = 8.3 Hz, H-14), 6.97 (d, 1H, J = 2.6 Hz, H-11), 6.73 (dd, 1H, J = 2.6, J = 8.33 Hz, H-13), 3.75 (s, 3H, H-OCH_3), 3.60 (s, 3H, H-CO_2CH_3), 2.90 (d × q, 1H), 2.70–2.84(m,4H), 2.56(m, 2H), 2.09(dt, 1H),1.82(s, 3H).

^{13}C NMR ($CDCl_3$): 197.2, 172.2, 158.5, 155.0, 138.4, 131.4, 129.4, 129.0, 112.6, 112.1, 55.2, 52.7, 51.2, 34.8, 33.8, 29.3, 27.8, 11.1.

ESI-MS(+): 323 $(M + Na)^+$.

HR ESI-MS(+): 301.1428$[M + H]^+$(calculated 301.1434)

6-Methoxy-1,1-dimethyl-2-oxo-1,3,4,9-tetrahydro-2H-phenanthrene-4a-carboxylic acid methyl ester 13

Compound **12** (260 mg, 0.87 mmol) was added to a solution of ^{t}BuOK (100 mg, 0.9 mmol) in ^{t}BuOH (10 mL) at 50–60°C. The mixture was stirred for another 30 min. Then, methyl iodide (128 mg, 0.9 mmol) in dry THF (5 mL) was added slowly. The mixture was stirred for another 3 h. After being cooled to room temperature, the mixture was acidified to pH 4 with 1 N hydrochloric acid. The mixture was diluted with ether (100 mL). The ether layer was washed with 5% $NaCO_3$, water, brine, and dried over sodium sulfate. After removal of the solvent under reduced pressure, purification by vacuum column chromatography on silica (eluant: petroleum ether/ethyl acetate 8 : 1) gave the product **13** (167 mg, 61% yield) yield as colorless crystalline.

m.p.: 112–114°C

IR: 2946, 1715, 1606, 1504, 1453, 1227, 826

^{1}H NMR ($CDCl_3$): 7.08 (d, 1H, J = 8.38 Hz), 6.92(d, 1H, J = 2.46 Hz), 6.80(dd, 1H, J = 2.51 Hz, J = 8.39 Hz), 6.12(dd, 1H, J = 3.01 Hz, J = 4.72 Hz), 3.79(s, 3H, OCH_3), 3.58(s, 3H, CO_2CH_3), 3.49(dd, 1H, J = 2.26 Hz, J = 22.6 Hz), 3.46(d, 1H, J = 4.8 Hz), 3.12(m, 1H), 3.02(m, 1H), 2.47(m,1H), 1.98(m, 1H), 1.35(s, 3H), 1.26(s, 3H);

^{13}C NMR ($CDCl_3$): 213.0, 174.5, 158.2, 139.6, 137.7, 129.0, 124.8, 122.5, 113.4, 111.0, 55.2, 52.4, 51.1, 49.1, 35.4, 34.1, 29.6, 27.4, 24.7.

ESI-MS(+): 317 $(M + Na)^+$.

HR ESI-MS(+): 337.1415$[M + Na]^+$(calculated 337.1410)

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