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A short synthetic route to biologically active (±)-daurichromenic acid as highly potent anti-HIV agent†

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The efficient total synthesis of biologically interesting (±)-daurichromenic acid is accomplished starting from 2,4-dihydroxy-6-methylbenzoic acid or 2,4-dihydroxy-6-methylbenzaldehyde in one or two steps.

Introduction

Daurichromenic acid (**1**) was isolated from the leaves and twigs of *Rhododendron dauricum*, a plant found in areas of northern China, eastern Siberia, and Hokkaido, Japan (Fig. 1).[1] The dried leaves of this plant are known as "manshanfong" in China and are used in medicines for as an expectorant and for the treatment of acute–chronic bronchitis.[2] Rhododaurichromanic acid A (**2**) and rhododaurichromanic acid B (**3**) were also isolated from the same plant.[3] Daurichromenic acid (**1**) has shown highly potent anti-HIV activity with an EC_{50} of 0.00567 μg mL^{-1} and a therapeutic index (TI) of 3710.[1] Rhododaurichromanic acid A (**2**) has also shown potent anti-HIV activity with an EC_{50} value of 0.37 μg mL^{-1} and a TI of 91.9.[1]

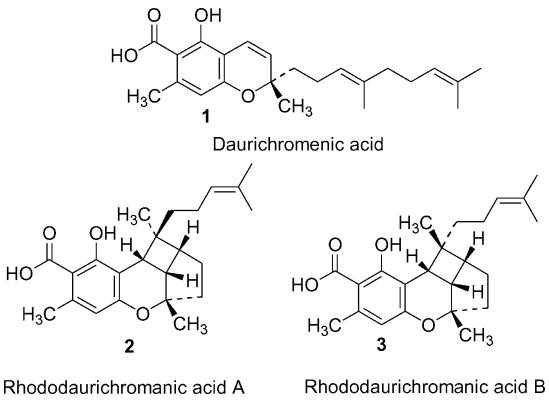
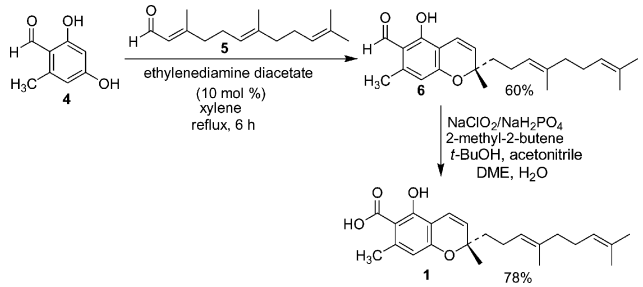


Fig. 1

The total synthesis of daurichromenic acid (**1**), rhododaurichromanic acid A (**2**), and rhododaurichromanic acid B (**3**) has been already reported by other groups.[4–6] The synthesis of the methyl ester of daurichromenic acid was first accomplished by Knoevenagel condensation followed by an electrocyclization reaction starting from 5-methyl-1,3-cyclohexanedione with *trans*,*trans*-farnesal in the presence of piperidine and Ac_2O using a sealed tube in 3 steps (22%, overall yield) by Hsung.[4] However, he was not able to find suitable reaction conditions of hydrolysis of methyl ester to complete a total synthesis of daurichromenic acid (**1**). The hydrolysis of the methyl and ethyl ester of **1** has been already reported to have a problem by two groups.[4–5] In most cases, decarboxylation occurred readily. The other concise total synthesis of daurichromenic acid (**1**) has been reported by Jin.[5] Daurichromenic acid (**1**) was accomplished in 5 steps (49%, overall yields) starting from orcinol. The key step in the synthetic strategy involves a microwave-assisted tandem condensation and intramolecular S_N2'-type cyclization in the presence of $CaCl_2$ and triethylamine. Further conversion of **1** to **2** and **3** was also accomplished by Jin utilizing photochemical reaction. More recently, another concise synthesis of **1** has been accomplished in 4 steps (6%, overall yields) from ethyl acetoacetate and ethyl crotonate by Wilson.[6] Although there are currently several methods available to synthesize daurichromenic acid (**1**), rhododaurichromanic acid A (**2**), and rhododaurichromanic acid B (**3**), these synthetic approaches have been limited due to long reaction steps, low yields, and stoichiometric amounts of the catalyst, and harsh reaction conditions in relation to sealed tube or microwave irradiation. The necessity for overcoming these problems has prompted research for improved synthetic approaches of daurichromenic acid (**1**). We report herein very efficient total synthesis of daurichromenic acid (**1**) starting from readily available 2,4-dihydroxy-6-methylbenzaldehyde (**4**) or 2,4-dihydroxy-6-methylbenzoic acid. (**7**)

Results and discussion

The synthesis of the benzopyran skeleton as a core of daurichromenic acid (**1**) was first examined from 2,4-dihydroxy-6-methylbenzaldehyde (**4**) as shown in Scheme 1. In order to avoid a hydrolysis reaction, 2,4-dihydroxy-6-methylbenzaldehyde (**4**) was selected as a starting material.[7] The methods for the preparation of 2*H*-benzopyrans have been reported by many groups.[8] Among these, the reaction conditions using $Ca(OH)_2$–EtOH or pyridine at 140 °C described by Shigemasa[8c] or Zamarlik[8f] appeared to be quite promising for the synthesis of benzopyrans. However, reaction of **4** with *trans*,*trans*-farnesal (**5**) in the presence of $Ca(OH)_2$–EtOH or in refluxing pyridine gave no expected product **6**. Thus, we investigated the possibility of the use of other catalysts to furnish **6**. The result was observed when reaction was treated under ethylenediamine diacetate as a catalyst. Reaction of **4** with *trans*,*trans*-farnesal (**5**) in the



Scheme 1

† Electronic supplementary information (ESI) available: NMR spectra. See http://dx.doi.org/10.1039/b508577b

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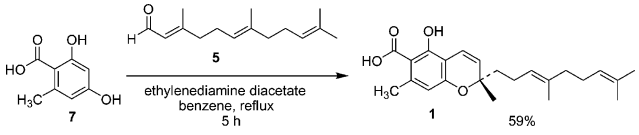
presence of 10 mol% ethylenediamine diacetate in refluxing xylene for 6 h afforded product **6** in 60% yield. It has been demonstrated that ethylenediamime diacetate-catalyzed reaction of 1,3-dicarbonyl compounds with enals readily afforded 2*H*-pyrans by Tietze.[9] However, ethylenediamime diacetate-catalyzed reaction of phenolic compounds with α,β-unsaturated aldehydes has not been reported. To complete the total synthesis, cycloadduct **6** was reacted under several oxidants. Oxidation of **6** with Jones' reagent,[10] Ag_2O–NaOH,[11] and oxone[12] gave no expected product **1**. Fortunately, reaction of **6** with buffered sodium chlorite[13] at room temperature for 10 h led to daurichromenic acid (**1**) in 78% yield. The spectroscopic data of synthetic material **1** are in agreement with those reported in the literature.[1]

Next, in order to demonstrate the novelty and usefulness of ethylenediamine diacetate as a new catalyst in the synthesis of daurichromenic acid (**1**), a one step reaction was attempted starting from 2,4-dihydroxy-6-methylbenzoic acid (**7**) as shown in Scheme 2.[14] Reaction of **7** with *trans*,*trans*-farnesal (**5**) in the presence of 10 mol% ethylenediamine diacetate in refluxing benzene for 5 h gave adduct **1** in 59% yield. The spectroscopic data of our synthetic material **1** are in agreement with those reported in the literature.[1]



Scheme 2

In conclusion, the concise total synthesis of daurichromenic acid (**1**) has been accomplished in 2 steps from readily available material, 2,4-dihydroxy-6-methylbenzaldehyde (**4**). The overall yield is 47%. Also, one step synthesis of **1** has been carried out from **7** in 59% yield. Further synthetic approaches of the analogues of **1** are in progress to sight structure–activity relationships of this potent anti-HIV lead compound.

Experimental

All experiments were carried out under a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR spectra were recorded on a Bruker Model ARX (300 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker Model ARX (75 MHz) spectrometer. Refer to the supplementary information for details of the NMR spectra. IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. HRMS mass spectra were carried out by Korea Basic Science Institute.

5-Hydroxy-2,7-dimethyl-2-(4,8-dimethyl-3*E*,7-nonadienyl)-2*H*-chromene-6-carbaldehyde (6)

2,4-Dihydroxy-6-methylbenzaldehyde (**4**) (456 mg, 3 mmol) and *trans*,*trans*-farnesal (**5**) (792 mg, 3.6 mmol) were dissolved in xylene (20 mL), and ethylenediamine diacetate (48 mg, 0.3 mmol) was added at room temperature. The mixture was refluxed for 6 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane–ethyl acetate (15 : 1) to give product **6** (637 mg, 60%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 1.64 (s, 3H), 1.60–1.82 (m, 2H), 1.85–2.11 (m, 6H), 2.44 (s, 3H), 5.03–5.10 (m, 2H), 5.46 (d, 1H, J = 10.1 Hz), 6.13 (s, 1H), 6.67 (d, 1H, J = 10.1 Hz), 9.99 (s, 1H), 12.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 18.1, 18.7, 23.0, 26.1, 27.0, 27.7, 39.9, 42.1, 81.0, 107.3, 111.4, 113.5, 116.2, 124.0, 124.7, 126.7, 131.7, 135.9, 144.0, 161.0, 161.5, 193.2; IR (neat) 2967, 2926, 1640, 1568, 1483, 1451, 1385, 1294, 1252, 1157, 1063, 1003, 897 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{30}O_3$: 354.2195. Found: 354.2196.

(±)-Daurichromenic acid (1)

Oxidation of 6. To a solution of the aldehyde **6** (200 mg, 0.56 mmol) in *t*-butanol (3 mL), acetonitrile (3 mL), 2-methyl-2-butene (2 mL), and DME (1 mL) was added NaH_2PO_4 (336 mg, 2.80 mmol) and $NaClO_2$ (253 mg, 2.80 mmol, dissolved in 1 mL of water) at 0 °C. The resulting mixture was warmed slowly to room temperature and stirred for 12 h. Brine (15 mL) was added, and the resultant solution was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concenturated *in vacuo*. The crude product was then purified by flash chromatography using hexane–ethylacetate (1 : 1) as the eluant to afford **1** (163 mg, 78%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.55 (s, 3H), 1.57 (3H, s), 1.65 (s, 3H), 1.70–1.80 (m, 2H), 1.86–2.12 (m, 6H), 2.51 (s, 3H), 5.03–5.10 (m, 2H), 5.46 (d, 1H, J = 10.1 Hz), 6.23 (s, 1H), 6.71 (d, 1H, J = 10.1 Hz), 11.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 17.7, 22.6, 24.6, 25.7, 26.8, 27.2, 39.7, 41.7, 80.3, 103.6, 107.0, 112.3, 116.7, 129.9, 124.4, 126.5, 131.4, 135.6, 144.5, 159.1, 160.7, 176.3; IR (neat) 2926, 1620, 1454, 1381, 1269, 1177, 908 cm^{-1}; HRMS m/z (M^+) calcd for $C_{23}H_{30}O_4$: 370.2144. Found: 370.2142.

Cycloaddition of 7. 2,4-Dihydroxy-6-methylbenzoic acid (**7**) (168 mg, 1.0 mmol) and *trans*,*trans*-farnesal (**5**) (264 mg, 1.2 mmol) were dissolved in benzene (20 mL), and ethylenediamine diacetate (18 mg, 0.1 mmol) was added at room temperature. The mixture was refluxed for 5 h and then cooled to room temperature. Removal of solvent at reduced pressure left an oily residue, which was then purified by column chromatography on silica gel using hexane–ethyl acetate (1 : 1) to give product **1** (218 mg, 59%).

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