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Syntheses and X-Ray Crystal Structures of Cassiferaldehyde and Analogs

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SYNTHESES AND X-RAY CRYSTAL STRUCTURES OF CASSIFERALDEHYDE AND ANALOGS

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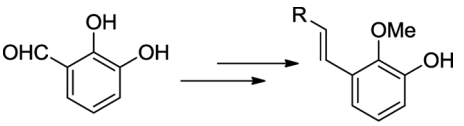
GRAPHICAL ABSTRACT



R = CHO (cassiferaldehyde), COMe, COPh, CO_2Me, CO_2Et, CO_2H, and CN

Abstract *Cassiferaldehyde, a recently discovered naturally occurring tyrosinase inhibitor, and six of its analogs, in which the aldehyde group has been replaced by various other functionalities, have been synthesized by a short and simple sequence starting from 2,3-dihydroxybenzaldehyde. Single-crystal x-ray structures of cassiferaldehyde as well as its methyl ketone, nitrile, and carboxylic acid analogs are reported.*

Keywords Alkylation; bioorganic chemistry; natural products; phenols; Wittig reaction

INTRODUCTION

Cinnamomum cassia Blume (Lauraceae), which is widely distributed in East Asia, has been a source of many natural products with a broad range of biological activity.[1] The twigs of this species have been used in traditional Chinese medicine to treat a variety of ailments.[2] In the course of a study to screen plants for tyrosinase inhibition, it was recently reported that the methanolic extract of the twigs of *C. cassia* afforded several new phenolics including cassiferaldehyde (**3a**), which was found to be a potent inhibitor of the enzyme.[3] Tyrosinase is known to play a key role in the synthesis of melanin and has been implicated as a participant in the oxidative stress chemistry that leads to Parkinson's disease.[4] Thus, tyrosinase inhibitors appear to offer the potential for treating this debilitating ailment which, after Alzheimer's, is the most common neurodegenerative disorder, affecting about 1–2% of the population more than 65 years of age.[5]

Herein we report a simple syntheses of cassiferaldehyde and analogs in which the aldehyde functionality has been substituted by ketone, ester,

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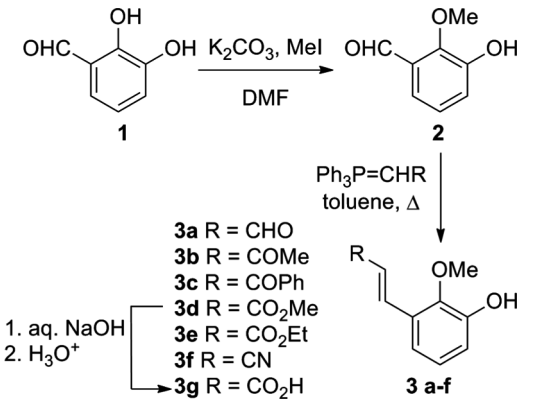

Scheme 1. Syntheses of cassiferaldehyde and analogs.

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nitrile, and carboxylic acid groups, starting from 2,3-dihydroxybenzaldehyde (**1**, Scheme 1). In the first step, the procedure of Boger and coworkers was used to selectively methylate the hydroxy group that is ortho to the aldehyde to afford 3-hydroxy-2-methoxybenzaldehyde (**2**).[6] This selectivity is made possible by the ortho hydroxy group having a lower *p*Ka than the one that is meta.[7] In the subsequent step, we adapted a recently published procedure[8] to react **2** with a host of stable, commercially available Wittig reagents bearing electron-withdrawing groups to obtain **3a**–**3f**. The carboxylic acid derivative **3g** was prepared by hydrolyzing the methyl ester analog **3d**. After purification by column chromatography, the (unoptimized) yields for the Wittig reactions ranged from 34% for cassiferaldehyde (**3a**) to 89% for the ethyl ester analog **3e**. The melting point of cassiferaldehyde that we prepared (119–122 °C) was higher than that reported in the literature (78–80 °C).[3] It should be noted, however, that our material was crystalline, whereas the naturally occurring version was an amorphous powder.[3] In all cases, except for **3f** (R=CN), an analysis of the ^{1}H NMR spectra of the crude products revealed an overwhelming preference for the *E* isomers. In the case of **3f**, however, the *Z* isomer was favored over *E* by a margin of 2:1.

Slow diffusion of pentane into a solution of **3a** in dichloromethane provided crystals suitable for analysis by x-ray crystallography.[9] The same approach was used to grow crystals of **3b**. Slow evaporation of the fractions from column chromatography (1:9 ethyl acetate–hexanes) also provided single crystals of **3f** appropriate for structure determination. We were unable, however, to crystallize the phenyl ketone analog **3c** and the two esters, **3d** and **3e**, which were viscous oils. Refluxing the methyl ester analog (**3d**) in aqueous sodium hydroxide followed by an acidic workup did afford the solid carboxylic acid derivative **3g**. Recrystallization of **3g** from chloroform-ethyl acetate gave crystals amenable to x-ray analysis. The crystal structures of these four compounds are shown in Figure 1.[10] Some of the key crystallographic parameters are shown in Table 1. In all four structures the *E* stereochemistry about the double bond is evident and the methoxy group is twisted away from the plane of the aryl ring.

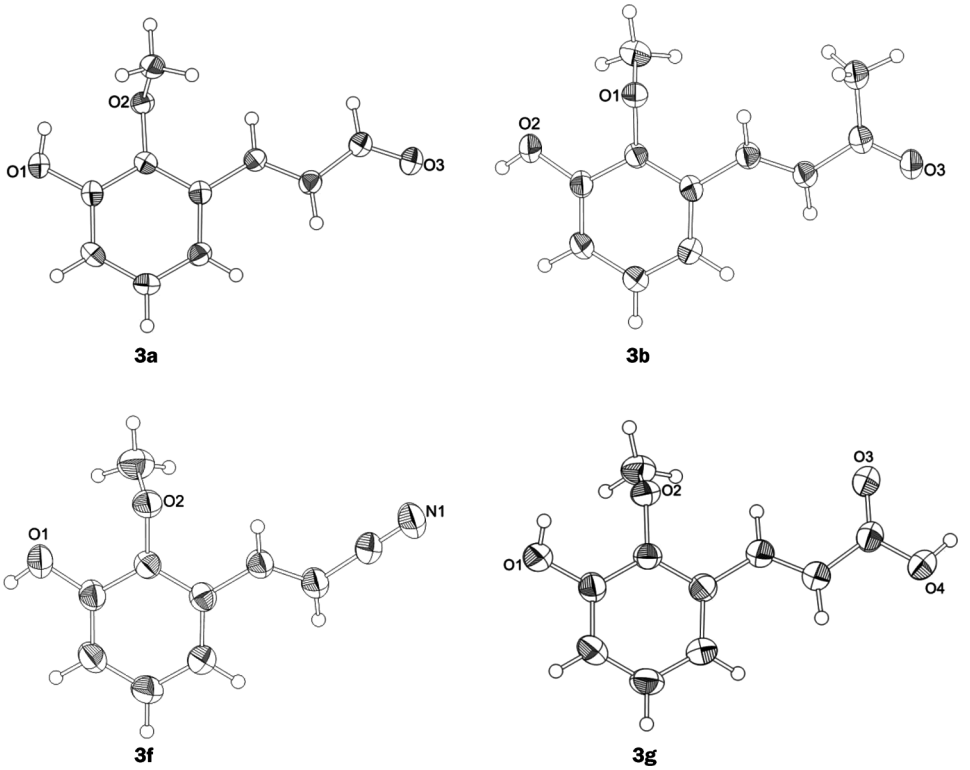

Figure 1. X-ray crystal structures of cassiferaldehyde (**3a**), and its methyl ketone (**3b**), nitrile (**3f**), and carboxylic acid (**3g**) analogs.

Table 1. Selected crystallographic data for **3a, 3b, 3f**, and **3g**

Entry	3a	3b	3f	3g
Chemical formula	$C_{10}H_{10}O_3$	$C_{11}H_{12}O_3$	$C_{10}H_9NO_2$	$C_{10}H_{10}O_4$
Formula weight	178.8	192.21	175.18	194.18
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic
Space group	P2(1)	P-1	P2(1)/c	P-1
Unit cell dimensions	a = 6.54 Å, α = 90°	a = 6.73 Å, α = 69.14°	a = 7.28 Å, α = 90°	a = 4.90 Å, α = 80.74°
	b = 6.68 Å, β = 91.06°	b = 7.84 Å, β = 76.63°	b = 8.27 Å, β = 91.37°	b = 7.45 Å, β = 85.68°
	c = 9.87 Å, γ = 90°	c = 10.32 Å, γ = 86.45°	c = 14.84 Å, γ = 90°	c = 13.01 Å, γ = 79.87°
Volume	431.1 Å[3]	494.2 Å[3]	893.0 Å[3]	460.59 Å[3]
Z	2	2	4	2
Final R indices [I > 2sigma(I)]	R1 = 0.0295, wR2 = 0.0779	R1 = 0.0470, wR2 = 0.1226	R1 = 0.0446, wR2 = 0.1263	R1 = 0.0436, wR2 = 0.1190
R indices (all data)	R1 = 0.0300, wR2 = 0.0782	R1 = 0.0641, wR2 = 0.1364	R1 = 0.0481, wR2 = 0.1318	R1 = 0.0535, wR2 = 0.1295

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EXPERIMENTAL

General Procedure for Syntheses of 3a–3f

3-Hydroxy-2-methoxybenzaldehyde[6] (**2**, 1 mmol) and the Wittig reagent (1.2 equivalents) in toluene (1 mL) were magnetically stirred and heated in an oil bath, which was maintained at 80 to 85 °C, for 1 h. After evaporation of solvent, the reaction mixture was subjected to flash chromatography over silica gel using ethyl acetate–hexanes (1:9) as eluent. In all cases, except **3f**, fractions containing the pure *E* isomers were obtained initially followed by later fractions that also included minor amounts of *Z* (in addition to *E*, which was predominant). In the case of the cyano analog **3f**, the *E* and *Z* isomers, which were formed in comparable amounts, could be separated and purified individually. Yields and characterization data are given.

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Cassiferaldehyde (3a)

Yellow solid; yield: 34%; mp: 119–122 °C (lit.[3] 78–80 °C); ^{1}H NMR (500 MHz, $CDCl_3$): 9.74 (d, $J = 7.7$ Hz, 1H), 7.71 (d, $J = 16.1$ Hz, 1H), 7.19–7.00 (m, 3H), 6.79 (dd, $J = 16.1$, 7.7 Hz, 1H), 5.80 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 194.1, 149.5, 146.9, 146.4, 130.1, 127.5, 125.4, 119.8, 118.7, 62.4; FTIR (ATR): 3335, 2840, 1661, 1646, 1134 cm^{-1}; MS (EI, 70 eV): $m/z = 178$, 147, 107. Anal. calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.15; H, 5.86.

Methyl Ketone Analog (3b)

Colorless solid; yield: 69%; mp: 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.76 (d, $J = 16.4$ Hz, 1H), 7.15–7.08 (m, 1H), 7.06–7.01 (m, 2H), 6.78 (d, $J = 16.4$ Hz, 1H), 6.16 (s, 1H), 3.84 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 198.9, 149.5, 146.6, 137.8, 128.5, 127.9, 125.2, 119.3, 118.0, 62.3, 27.5; FTIR (ATR): 3088, 1670, 1621, 1264 cm^{-1}; MS (EI, 70 eV): $m/z = 192$, 177, 161, 134. Anal. calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.84; H, 6.48.

Phenyl Ketone Analog (3c)

Colorless oil; yield: 68%; ^{1}H NMR (500 MHz, $CDCl_3$): 8.08–7.97 (m, 3H), 7.68–7.57 (m, 2H), 7.55–7.47 (m, 2H), 7.25–7.19 (m, 1H), 7.11–7.00 (m, 2H), 5.87 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 190.6, 149.5, 146.7, 139.1, 138.1, 132.9, 128.7, 128.5, 128.4, 125.2, 123.7, 119.8, 117.7, 62.4; FTIR (film): 3368, 1659, 1582, 1285 cm^{-1}; MS (EI, 70 eV): $m/z = 254$, 223, 165, 134. Anal. calcd. for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.37; H, 5.83.

Methyl Ester Analog (3d)

Colorless oil; yield: 68%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.89 (d, $J = 16.1$ Hz, 1H), 7.04 (m, 3H), 6.51 (d, $J = 16.1$ Hz, 1H), 5.77 (s, 1H), 3.82 (2 overlapping singlets, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): 167.5, 149.3, 146.3, 139.1, 127.8, 125.2, 119.6, 119.5, 117.5, 62.4, 51.8; FTIR (film): 3396, 1698, 1634, 1286 cm^{-1};

MS (EI, 70 eV): $m/z = 208$, 177, 162, 134. Anal. calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.62; H, 6.08.

Ethyl Ester Analog (3e)

Colorless oil; yield: 89%; ^{1}H NMR (500 MHz, $CDCl_3$): 7.88 (d, $J = 16.1$ Hz, 1H), 7.14–6.89 (m, 3H), 6.51 (d, $J = 16.1$ Hz, 1H), 5.77 (s, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.83 (s, 3H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 167.0, 149.3, 146.3, 138.8, 127.9, 125.1, 120.1, 119.5, 117.4, 62.4, 60.6, 14.3; FTIR (film): 3392, 1712, 1633, 1286 cm^{-1}; MS (EI, 70 eV): $m/z = 222$, 191, 177, 163. Anal. calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.98; H, 6.77.

Nitrile Analog (3f)

Colorless solid; yield: 86%.

***E* Isomer.** Mp: 149–151 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.58 (d, $J = 16.8$ Hz, 1H), 7.13–6.92 (m, 3H), 6.01 (d, $J = 16.8$ Hz, 1H), 5.61 (s, 1H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 149.4, 145.9, 145.2, 127.0, 125.5, 119.0, 118.6, 118.2, 98.2, 62.3; FTIR (ATR): 3291, 2228, 1610, 1581, 1283 cm^{-1}; MS (EI, 70 eV): $m/z = 175$, 160, 147, 132.

***Z* Isomer.** Mp: 57–60 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.66 (d, $J = 7.8$ Hz, 1H), 7.44 (d, $J = 12.2$ Hz, 1H), 7.18–7.00 (m, 2H), 5.69 (s, 1H), 5.54 (d, $J = 12.2$ Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): 149.0, 145.9, 142.9, 127.1, 125.3, 119.8, 118.5, 117.1, 96.7, 62.7; FTIR (ATR): 3352, 2925, 2226, 1613, 1568, 1210 cm^{-1}; MS (EI, 70 eV): $m/z = 175$, 160, 147, 132.

Anal. calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found (for E/Z mix): C, 68.63; H, 5.52; N, 7.69.

Carboxylic Acid Analog 3g

An E/Z mixture (3:1) of the methyl ester analog (**3d**, 296 mg, 1.4 mmol) was refluxed for 1 h in 2.5 M aqueous NaOH. The reaction mixture was cooled and extracted with ether (15 mL), and the aqueous layer was acidified with 6 M aqueous HCl. The carboxylic acid was extracted from the aqueous layer with ether (3×25 mL), and this second set of ether extracts was combined, washed with water, and freed of solvent to obtain a white solid. Recrystallization of this solid from aqueous ethanol gave **3g** as the *E* isomer.

Colorless solid; yield: 53%; mp: 217–220 °C.

^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 12.36$ (s, 1H), 9.57 (s, 1H), 7.77 (d, $J = 16.2$ Hz, 1H), 7.15 (d, $J = 7.4$, 1H), 7.00–6.85 (m, 2H), 6.46 (d, $J = 16.1$ Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): $\delta = 168.2$, 150.9, 147.1, 139.0, 128.3, 124.7, 120.2, 119.1, 118.2, 61.0; FTIR (ATR): 3412, 2602, 1684, 1622, 1201 cm^{-1}; MS (EI, 70 eV): $m/z = 194$, 177, 163, 147, 134. Anal. calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.79; H, 5.16.

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General Procedure for X-Ray Structure Determination

X-ray data were collected at 173 K for **3a** and **3b**, and ambient temperature for **3f** and **3g**, on a Bruker Smart Apex charge-coupled device (CCD) diffractometer using graphite monochromated Mo Kα radiation ($\gamma = 0.71073$ Å) and processed with the Bruker Apex2 suite of programs.[11] The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multiscan method (SADABS).[12] All structures were solved by direct methods and refined by full-matrix least-squares on F^2, using the Bruker SHELXTL software package.[11,13] All nonhydrogen atoms were refined anisotropically, and the hydrogens were calculated on a riding model. The software program enCIFer[14] was used in conjunction with the checkCIF/Platon facility of the International Union of Crystallography to validate cif files. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre and assigned the following deposition numbers: CCDC 771896, 771897, 771898, and 771899 for **3a, 3b, 3f**, and **3g** respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).

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