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Efficient, Scalable Syntheses of Ginkgolic Acids

Joshua L. Alterman¹ and George A. Kraus¹

Abstract
Ginkgolic acids were directly synthesized from 6-methylsalicylic acid using a sequence involving protection of the phenol and acid as methoxymethyl ethers and esters, lateral alkylation and deprotection under mild aqueous acid conditions.

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Ginkgolic acid C15:1 (1) and ginkgolic acid C15:0 (2) are natural acids isolated from Ginkgo biloba (Figure 1).¹ Ginkgolic acid is a component of a botanical extract which shows pleiotropic effects including antitumor and anti-HIV activities.² The synthesis of (1) has been reported by Martin in 2018 using a Heck-based strategy.³ Several researchers used Wittig-based strategies.⁴⁻⁷ The lateral alkylation strategy presented herein, also used by Tyman,⁸ utilizes commercially available and stable reagents such as (3) and is amenable to scale up.

Protection of 6-methyl salicylic acid (3) with in situ derived chloromethyl methyl ether provided ester (4) as shown in Scheme 1.⁹ A variety of bases were evaluated for the deprotonation of (4). Ultimately, treatment of (4) with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in tetrahydrofuran (THF) at −78°C, followed by the addition of the acetylenic iodide (5),¹⁰ and warming to ambient temperature overnight afforded the alkynyl ester (6) in 60% yield. Reduction of the alkyne using hydrogen and the Lindlar’s catalyst followed by treatment with 1 N HCl to remove the protecting groups afforded (1) in 61% yield. The use of the methoxymethyl ether protecting groups increased the solubility of (4) and enables easy global deprotection to 1.

The reaction of the anion of (4) with 1-iodotetradecane followed by deprotection generated (2) in 61% yield as shown in Scheme 2. Iodotetradecane was prepared from the commercially available chloride in 90% yield using sodium iodide.

The synthesis of (1) and (2) in three or four steps constitutes a direct route to these biologically active compounds.¹¹ This direct pathway will enable the synthesis of (1), (2), and analogs for biological evaluation.

Experimental

Methoxymethyl-2-(Methoxymethoxy)-6-Methylbenzoate (4)
To 35 mL DMF was added (3) (893 mg, 5.86 mmol) and allowed to stir at 0°C for 15 minutes. Then 5 equivalents of NaH was added in 4 portions. The solution was brought from 0°C to r.t for 30 minutes, then cooled back to 0°C. Chloromethyl methyl ether, (1.4 mL, 3.14 equiv.), was added over 4 additions, every 15 to 20 minutes. Reaction was gently quenched with ice and sat. NH₄Cl and then extracted with ethyl acetate. After drying over Na₂SO₄, and concentrating in vacuo, the resulting oil was purified using silica gel chromatography (Hexane:Ethyl acetate, 3:7) affording a clear, colorless, oil (4) (1.13 g, 80% yield).

¹H NMR (400 MHz CDCl₃): δ (ppm) 7.23 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 5.47 (s, 2H), 5.18 (s, 2H), 3.58 (s, 3H), 3.47 (s, 3H), δ 2.34 (s, 3H).

Methoxymethyl-2-(Methoxymethoxy)-6-(Pentadec-8-yn-1-yl) Benzoate (6)
To oven dried reaction vessel tetramethylpiperidine (0.26 mL, 1.5 mmol) was added, followed by 6 mL of THF and

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was cooled to 0°C. Argon was then bubbled through the solution for ~5 minutes. Addition of $n$BuLi (0.60 mL, 1.5 mmol) was done dropwise, and the reaction allowed to reach room temperature (r.t.) for 25 minutes. The solution was then cooled to −78°C where (4) (238 mg, 0.991 mmol) in 2 mL of THF was slowly added and reacted for 71 minutes. Then (5) (548 mg, 1.7 mmol) in 2 mL of THF was chilled to −78°C, and syringed while cold. The reaction was let warm to room temperature overnight. The reaction was quenched with sat. NH$_4$Cl and extracted with ethyl acetate, dried over Na$_2$SO$_4$, and concentrated in vacuo. The resulting oil was purified using silica gel chromatography (Hexane:Ethyl acetate, 1:1) affording a clear, orange, oil (6) (0.260 g, 60% yield).

$^1$H NMR (400 MHz CDCl$_3$): δ (ppm) 7.26 (t, $J = 7.9$ Hz, 1H), 7.00 (d, $J = 8.1$ Hz, 1H), 6.89 (d, $J = 7.7$ Hz, 1H), 5.46 (s, 2H), 5.18 (s, 2H), 3.56 (s, 3H), 3.47 (s, 3H), 2.59 (t, $J = 7.8$ Hz, 2H), 2.13 (m, 4H), 1.60 (m, 4H), 1.51-1.22 (m, 16H), 0.88 (t, $J = 6.5$ Hz, 3H).

(Z)-2-Hydroxy-6-(Pentadec-8-en-1-yl)Benzoic acid (1)

A flask containing (6) (208 mg, 0.48 mmol), in 5 mL of methanol, with 10 µL of quinoline, was sparged with Argon. Lindlar’s catalyst was added, and then hydrogen was bubbled through via balloon. Lindlar’s catalyst was removed over a pad of Celite, and the filtrate condensed. Treatment of the resulting oil with 1 M HCl in the presence of isopropyl alcohol for 5 hours afforded (1) (0.101 g, 61% yield).

$^1$H NMR (400 MHz CDCl$_3$): δ (ppm) 7.09 (t, $J = 7.8$ Hz, 1H), 6.67 (d, $J = 8.1$ Hz, 1H), 6.62 (d, 1H, $J = 7.5$ Hz), 5.32 (m, 2H), 2.95 (t, $J = 7.5$ Hz, 2H), 1.96 (m, 4H), 1.50 (m, 2H), 1.32-1.18 (m, 17H), 0.84 (t, $J = 6.6$ Hz, 3H).

LRMS (ESI-QTOF) calcd. for C$_{22}$H$_{34}$O$_3$ [M-H]$^-$ 345.2435, found 345.2445.

2-Hydroxy-6-Pentadecylbenzoic Acid (2)

To an oven dried flask tetramethylpiperidine (0.34 mL, 2.0 mmol) was added, followed by 2 mL of THF and was cooled to 0°C. Argon was then bubbled through the solution for ~5 minutes. Addition of $n$BuLi (0.80 mL, 2.0 mmol) was done dropwise, and the flask allowed to reach r.t. for 26 minutes. It was then cooled to −78°C where (4) (291 mg, 1.21 mmol) in 2 mL of THF was slowly added and reacted for 70 minutes. 1-Iodotetradecane (778 mg, 2.4 mmol) in 2 mL of THF, was chilled to −78°C, and syringed while cold. The reaction was let warm to room temperature overnight. The reaction was acidified with 1 M HCl in the presence of isopropyl alcohol for 5 hours and extracted with ethyl acetate, dried over Na$_2$SO$_4$, and then concentrated in vacuo. The resulting solid was purified using silica gel chromatography (Hexane:Ethyl acetate, 1:1) affording a brownish orange solid (2) (0.257 g, 61% yield).

$^1$H NMR (400 MHz CDCl$_3$): δ (ppm) 11.12 (s, OH), 7.29 (t, $J = 8.2$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.72, (d, $J = 7.6$ Hz, 1H), 2.88 (t, $J = 7.5$ Hz, 2H), 1.53-1.15 (m, 26H), 0.88 (t, $J = 7.5$ Hz, 3H).

Iodotetradecane

To an oven dried flask 1-chlorotetradecane (2.35 g, 14.4 mmol) was added, followed by 50 mL of acetone and NaI (3.01 g, 20.1 mmol), and refluxed for 48 hours. Then the reaction was cooled to 0°C and extracted with hexane and concentrated in vacuo. Residual yellow discoloration was removed over a pad of silica affording a clear, colorless, oil (4.20 g, 90% yield).

$^1$H NMR (400 MHz CDCl$_3$): δ (ppm) 3.18 (t, $J = 7.1$ Hz, 2H), 1.82 (pent, $J = 7.2$ Hz, 2H), 1.43-1.21 (m, 22H), 0.88 (t, $J = 6.8$ Hz, 3H).

Figure 1. Structures for ginkgolic acids C15:1 (1) and C15:0 (2).

Scheme 1. Synthesis of 1.

Scheme 2. Synthesis of (2).
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Declaration of Conflicting Interests

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