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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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lateral alkylation, anti-HIV, direct synthesis

### Disciplines

Organic Chemistry

### Comments

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# Efficient, Scalable Syntheses of Ginkgolic Acids

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Joshua L. Alterman<sup>1</sup> and George A. Kraus<sup>1</sup>

## 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).<sup>1</sup> Ginkgolic acid is a component of a botanical extract which shows pleiotropic effects including antitumor and anti-HIV activities.<sup>2</sup> The synthesis of (**1**) has been reported by Martin in 2018 using a Heck-based strategy.<sup>3</sup> Several researchers used Wittig-based strategies.<sup>4–7</sup> The lateral alkylation strategy presented herein, also used by Tyman,<sup>8</sup> 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.<sup>9</sup> 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  $-78^{\circ}\text{C}$ , followed by the addition of the acetylenic iodide (**5**),<sup>10</sup> 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 methoxy methyl 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.<sup>11</sup> 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  $0^{\circ}\text{C}$  for 15 minutes. Then 5 equivalents of NaH was added in 4 portions. The solution was brought from  $0^{\circ}\text{C}$  to r.t for 30 minutes, then cooled back to  $0^{\circ}\text{C}$ . 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.  $\text{NH}_4\text{Cl}$  and then extracted with ethyl acetate. After drying over  $\text{Na}_2\text{SO}_4$  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).

$^1\text{H NMR}$  (400 MHz  $\text{CDCl}_3$ ):  $\delta$  (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), 3.56 (s, 3H), 3.47 (s, 3H),  $\delta$  2.34 (s, 3H).

### Methoxymethyl-2-(Methoxymethoxy)-6-(Pentadec-8-yn-1-yl) Benzoate (**6**)

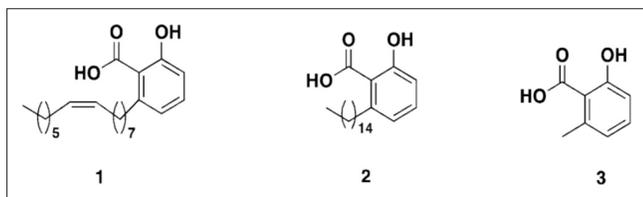
To oven dried reaction vessel tetramethylpiperidine (0.26 mL, 1.5 mmol) was added, followed by 6 mL of THF and

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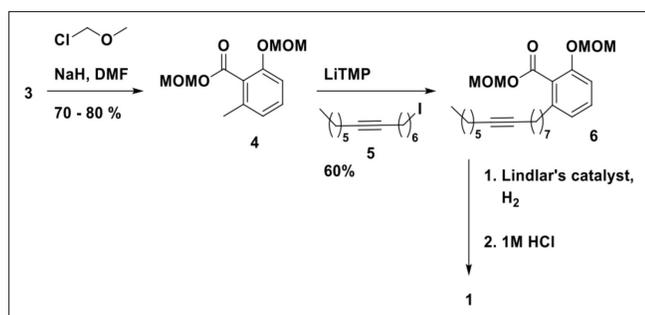
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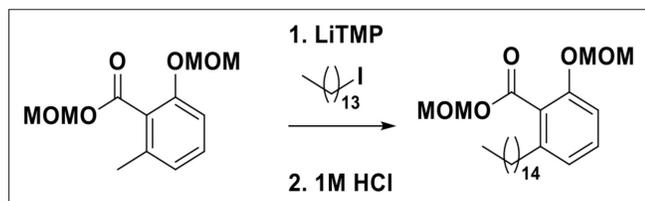




**Figure 1.** Structures for ginkgolic acids C15:1 (**1**) and C15:0 (**2**).



**Scheme 1.** Synthesis of **1**.



**Scheme 2.** Synthesis of (**2**).

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<sub>4</sub>Cl and extracted with ethyl acetate, dried over Na<sub>2</sub>SO<sub>4</sub>, 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).

<sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>): 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).

<sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>): 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<sub>22</sub>H<sub>34</sub>O<sub>3</sub> [M-H]<sup>-</sup> 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<sub>2</sub>SO<sub>4</sub>, 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).

<sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>): 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).

### 1-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).

<sup>1</sup>H NMR (400 MHz CDCl<sub>3</sub>): 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).

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## Declaration of Conflicting Interests

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