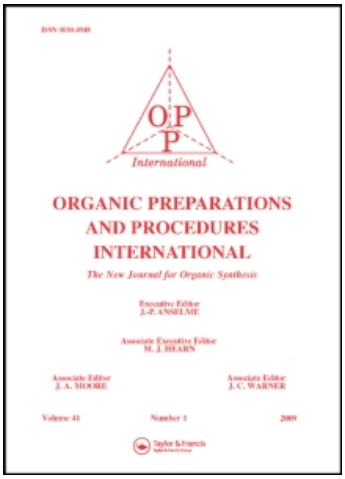

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FACILE AND EFFICIENT SYNTHESIS OF ISOLONGIFOLENONE

Shifa Wang[ab]; Aijun Zhang[c]
[a] Department of Entomology, Virginia Polytechnic Institute and State University, Virginia, VA, USA [b] College of Chemical Engineering, Nanjing Forestry University, Nanjing, Jiangsu, PR CHINA [c] Invasive Insect Biocontrol and Behavior Laboratory, BARC-West, USDA, ARS, Beltsville, MD, USA

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FACILE AND EFFICIENT SYNTHESIS OF ISOLONGIFOLENONE

Submitted by Shifa Wang[†,††] and Aijun Zhang*[,†††]
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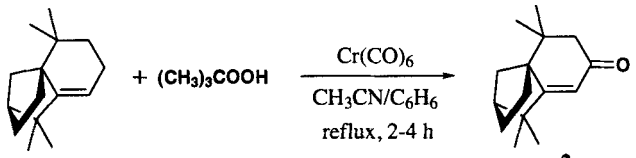
[†] *Department of Entomology*
Virginia Polytechnic Institute and State University
Blacksburg, Virginia, VA 24061, USA

[††] *College of Chemical Engineering, Nanjing Forestry University*
Nanjing, Jiangsu 21037, P. R. CHINA

[†††] *Invasive Insect Biocontrol and Behavior Laboratory*
BARC-West, USDA, ARS, Beltsville, MD 20705, USA
E-mail: aijun.zhang@ars.usda.gov

Isolongifolenone (**2**) is an important sesquiterpenoid in industry. Its derivatives have been widely used as fragrances in perfumes,[1] space sprays, cosmetics, detergents, deodorants, fabrics, fibres, and paper products.[2] In addition, (-)-isolongifolenone and its derivatives have been found to be active against tyrosinase, which is a multifunctional copper-containing enzyme for melanin biosynthesis in plants and animals.[3] They have been considered as clinically useful tyrosinase inhibitors for the treatment of some dermatological disorders associated with melanin hyper-pigmentation.[4] Moreover, saturated (-)-isolongifolenone (1,1,5,5-tetramethyloctahydro-2,4*a*-methanonaphthalen-7-one) has been used as a bridged core structure to prepare a chiral estrogen receptor ligand for use in regulation of fertility, prevention and treatment of breast cancer, and for menopausal hormone replacement.[5] Recently, isolongifolenone has been isolated as the natural product from crude extracts of the stems and leaves of *Humiria balsamifera* St. (Aubl.) Hill (Humiriaceae), which are distributed commonly in the Amazon and northeast regions of Brazil and have been found to possess antimalarial activity.[6]

Historically, isolongifolenone (**2**) has been obtained by the isomerization of longifolene, a bridged tricyclic sesquiterpene found in turpentine oil,[2b,7] to isolongifolene (**1**) followed by subsequent allylic oxidation using oxygen, air, or metal oxides.[8] However, these oxidative methods are ineffective involving long reaction times and low yields. In particular, the selectivity is not high in that double bound migration and epoxidation usually also occurred. The many unwanted by-products produced were difficult to separate from the desired product because of the similarity of their physical and chemical properties. This paper reports an alternative process for the preparation of (-)-isolongifolenone {(1*R*,8*S*)-2,2,7,7-tetramethyltricyclo[6.2.1.$0^{1,6}$]undec-5-en-4-one} (**2**) as the sole major product from (-)-isolongifolene (**1**), using *tert*-butyl hydroperoxide as the oxidant, chromium hexacarbonyl as the catalyst, and acetonitrile and benzene as solvent. This procedure requires shorter reaction time and results in high yield (≥82%) of product (**2**) in high purity (≥99.7%) (*Scheme 1*).

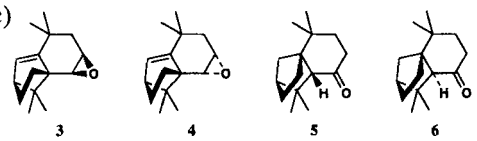


1 **Scheme 1** 2

Table 1. Oxidation of (-)-Isolongifolene under Varying Conditions[a]

Entry	Oxidants	Catalyst	Time (h)	Conversion (%)	Product ratios (%)[b,c] (2)	(3)	(4)	(5)	(6)	Others[d]
1	H_2O_2	$Cr(CO)_6$	1.0	18.7	35.3	23.5	11.5	16.4	7.7	5.6
2	H_2O_2	$Cr(CO)_6$	2.5	19.1	36.4	22.9	11.1	16.2	7.6	5.8
3	H_2O_2	$Cr(CO)_6$	18.0	46.6	37.7	14.4	6.2	23.4	7.4	10.9
4	CH_3COOOH	-	1.8	99.8	0.8	0	0	83.9	3.1	12.2
5	CH_3COOOH	$Cr(CO)_6$	1.5	100	0.5	0	0	80.2	4.6	14.7
6	$(CH_3)_3COOH$	-	1.0	17.9	75.4	2.5	2.4	7.3	7.8	4.6
7	$(CH_3)_3COOH$	-	4.0	37.5	79.8	1.7	1.3	6.4	6.1	4.7
8	$(CH_3)_3COOH$	-	16.0	70.8	84.7	0.9	0.8	2.9	4.0	6.7
9	$(CH_3)_3COOH$	-	21.0	84.8	84.7	0.7	0.6	3.2	4.0	6.8
10	$(CH_3)_3COOH$	-	23.5	95.1	77.1	0.1	0.1	2.4	3.0	17.3
11	$(CH_3)_3COOH$	$Cr(CO)_6$	0.5	35.2	66.2	1.1	0.9	1.1	5.1	25.6
12	$(CH_3)_3COOH$	$Cr(CO)_6$	1.0	88.7	85.0	1.5	0.7	1.1	2.7	9.0
13	$(CH_3)_3COOH$	$Cr(CO)_6$	1.5	97.0	88.6	1.3	0.6	1.0	2.4	6.1
14	$(CH_3)_3COOH$	$Cr(CO)_6$	2.0	98.9	90.7	1.3	0.6	1.2	2.1	4.1
15	$(CH_3)_3COOH$	$Cr(CO)_6$	2.5	99.5	91.5	1.4	0.7	2.2	1.2	3.0
16	$(CH_3)_3COOH$	$Cr(CO)_6$	3.0	99.6	91.7	1.5	0.8	1.5	1.9	2.6
17	$(CH_3)_3COOH$	$Cr(CO)_6$	3.5	100	93.0	1.4	0.8	2.1	1.1	1.2
18	$(CH_3)_3COOH$	$Cr(CO)_6$	4.0	100	93.2	1.5	1.0	2.3	----	2.0
19	$C_6H_5C(CH_3)_2OOH$	-	2.0	59.2	76.6	----	----	10.5	5.9	6.9
20	$C_6H_5C(CH_3)_2OOH$	-	4.5	73.4	76.6	1.0	1.1	7.8	6.3	7.2
21	$C_6H_5C(CH_3)_2OOH$	-	70.0	76.6	81.5	1.3	1.3	4.7	6.6	4.6
22	$C_6H_5C(CH_3)_2OOH$	$Cr(CO)_6$	1.0	65.3	88.9	----	----	2.0	4.9	4.2
23	$C_6H_5C(CH_3)_2OOH$	$Cr(CO)_6$	4.0	80.6	88.0	1.1	0.8	1.4	4.4	4.3
24	$C_6H_5C(CH_3)_2OOH$	$Cr(CO)_6$	21.0	86.3	88.3	1.3	1.0	0.6	5.6	3.2
25	$C_6H_5C(CH_3)_2OOH$	$Cr(CO)_6$	45.0	86.7	88.5	1.2	1.0	1.0	5.4	2.9

a) All chemicals were used in the same ratio. b)Determined by GC and GC-MS.

c) 

3 4 5 6

d) Consisted of several unidentified components

Successful conversion of isolongifolene (**1**) into isolongifolenone (**2**) depends on the selectivity of the allylic oxidation of the alkene in **1** into the α,β-unsaturated ketone in **2** without double bond migration or epoxidation. Our investigations involve the use of peroxides such as hydrogen peroxide, *tert*-butyl hydroperoxide, and cumene hydroperoxide as the oxidants, with or without chromium hexacarbonyl as the catalyst, which has been used to effectively convert unsaturated steroids into the corresponding α,β-unsaturated ketones.[9] The same amount of (-)-isolongifolene (**1**) was used as the starting material in the different reactions and the results are summarized in *Table 1*.

Peracetic acid (*Entries 4-5*) could efficiently oxidize isolongifolene (**1**) in less than 2 h, but isolongifolanone (**5**) was the main product, (–)-isolongifolenone (**2**) being less than 1%, and the product ratios were not influenced by the catalyst. Although (–)-isolongifolenone (**2**) was the predominant product with cumene hydroperoxide (*Entries 19-25*), 11-24% of other isomers were formed. Hydrogen peroxide (*Entries 1-3*) gave poor results, with varying amounts of **2** to **6** and other unidentified compounds being produced. A high degree of selectivity was observed in the conversion of isolongifolene (**1**) into isolongifolenone (**2**) by using *tert*-butyl hydroperoxide, chromium hexacarbonyl as the catalyst, and acetonitrile and benzene as solvent in a short reaction time (*Entries 11-18*). For example, the percent conversion was about 99% and 90% (–)-isolongifolenone (**2**) was formed after 2 h oxidation. At 3.5 h, (–)-isolongifolene (**1**) was completely oxidized and 93% (–)-isolongifolenone (**2**) was obtained. However, the percent conversion was only about 38% and less than 80% (–)-isolongifolenone (**2**) was detected in the oxidation products without the chromium hexacarbonyl catalyst after 4 h oxidation (*Entry 7*), indicating that the selectivity of allylic oxidation of isolongifolene was effectively influenced by this catalyst. It was also interesting to note that the catalytic activity of recovered chromium hexacarbonyl was not affected in the conversion of isolongifolene (**1**) into isolongifolenone (**2**) in the same oxidation process. The chromium hexacarbonyl has been successfully recycled in the same pot without any further treatment for the subsequent oxidation using 10% smaller amounts of isolongifolene and oxidant, *tert*-butyl hydroperoxide, resulting in the same yield and purity of isolongifolenone (**2**).

In summary, we have developed a facile and efficient method for the conversion of isolongifolene (**1**) to isolongifolenone (**2**). The process involves the use of *tert*-butyl hydroperoxide as the oxidant, chromium hexacarbonyl as the recyclable catalyst, and acetonitrile and benzene as solvent. Because *tert*-butyl hydroperoxide has a high thermal stability compared to other organic peroxides and is one of the safest organic peroxides,[10] this procedure could be easily scaled up for industrial production.

EXPRIMENTAL SECTION

NMR spectra were recorded in $CDCl_3$ (Aldrich) solution on a Bruker AV spectrometer at 400 MHz for ^1H, and 100 MHz for ^{13}C respectively. The chemical shifts are expressed in δ relative to

the residual solvent for ^1H ($CDCl_3$ at δ 7.25), or to the central peak of $CDCl_3$ ^{13}C signal (at 77.0 ppm). Gas chromatography electron impact (EI) mass spectrometry (GC-MS) was conducted using a 30 m x 0.25-mm id, 0.25-μm film-thickness capillary column (DB-5, J&W Scientific, Folsom, CA) with helium as carrier gas (38 cm/s). The initial temperature of the column was 50°C for 2 min, then programmed to 250°C at 15°C/min and held for 20 min. A 70 eV electron beam was employed for sample ionization. GC analyses were performed in the splitless mode using a 30 m x 0.32-mm id, 0.25-μm film-thickness capillary column (HP-5, J&W Scientific, Folsom, CA) with hydrogen as carrier gas (38 cm/s). The initial temperature of the column was 50°C for 2 min, then programmed to 250°C at 10°C/min and held for 20 min. Melting points were determined on a hot stage. Flash column chromatography was carried out on silica gel (230-400 mesh, Aldrich). Solvents and chemicals were obtained from Aldrich unless otherwise stated.

CAUTION: Chromium hexacarbonyl is a colorless solid (mp. 151-152°C) and is nearly insoluble in water and ethanol. It has a general toxic effect. LD_{50} is 100 mg/kg *iv* in mice.[11] Safety glasses, good ventilation, and gloves are recommended for personal protection.

Synthesis of Isolongifolenone 2.- A mixture of (-)-isolongifolene (300 mg, 1.47 mmol, purity 98% GC, bp. 255-256°C, Sigma, St. Louis, MO) and chromium hexacarbonyl (0.5 equiv., 161 mg, 0.73 mmol) in 4 mL of acetonitrile and 0.4 mL of benzene (benzene promotes the dissolution of (-)-isolongifolene into acetonitrile and expedites reaction) was refluxed under nitrogen or argon atmosphere until the chromium hexacarbonyl dissolved, and then *t*-butyl hydroperoxide (3.0 equiv., 70 wt. % in water, 0.61 mL, 4.40 mmol) was added dropwise. The resulting reaction mixture was gently refluxed for a period of time (2-4 hr) and the reaction was monitored by GC. After the peak of the starting (-)-isolongifolene (**1**) completely disappeared, the reaction mixture was cooled to room temperature using an ice-bath, the liquid phase was withdrawn by glass pipette and filtered through a sintered funnel. The precipitate (chromium hexacarbonyl) was washed with cold benzene (3 x 4 mL) and can be recycled in subsequent oxidations. The filtrate and benzene wash were combined, diluted with hexane (10 mL), washed with water (3 x 5 mL) and brine, then dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give 315.6 mg of crude product (yield 98%, purity 93.9%). The (-)-isolongifolenone obtained was purified by a flash chromatography on silica gel 60 Å using hexane-ethyl acetate (5:1 v/v) as eluent to provide 264 mg (1.21 mmol, 82% yield, 99.7% purity) of (-)-isolongifolenone (**2**) as a white semi-solid at room temperature, mp. 34°C (*lit*, mp. 39-40°C[2b]); $[\alpha]_D^{26}$ –153.30 (*c* 10.45, MeOH); ^1H-NMR ($CDCl_3$, 400 MHz): δ 0.94 (3H, s, CH_3), 1.00 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.96-1.28 (1H, m), 1.35 (1H, d, J = 10.2 Hz), 1.57 (1H, m), 1.62 (1H, dq, J = 10.2, 2.0 Hz), 1.67-1.73 (1H, m), 1.87 (1H, dd, J = 12.0, 4.0 Hz), 1.92 (1H, d, J = 4.0 Hz), 2.00 (1H, d, J = 16.0 Hz, O=CC-H), 2.33 (1H, d, J = 16.0 Hz, O=CC-H), 5.65 (1H, s, =C-H); ^{13}C-NMR ($CDCl_3$, 100 Hz): δ 24.26, 24.50, 25.32, 25.69, 26.91, 27.76, 34.36, 36.62, 44.00, 46.43, 49.83, 58.54, 116.78, 183.82, 200.10; EI-MS *m/z* (%): 218 $[M]^+$ (56), 203 (13), 189 (8), 175 (100), 162 (73), 147 (58), 133 (23), 119 (25), 105 (21), 91 (29), 77 (12), 69 (9), 55 (8).

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