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CHEMOTHERAPEUTIC AGENTS FROM NATURAL PRODUCT TEMPLATES: THE DESIGN AND SYNTHESIS OF NOVEL INDANONE ANALOGUES

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Abstract

Coumarin is a natural product found in many plants. Recently, simple coumarin analogues containing an α-methylene functional group have been synthesized and shown to exhibit cytotoxicity against cancer cell lines. The α,β-unsaturated carbonyl found in these analogues is thought to be responsible for their bioactivity. Other natural products containing this functional group have been shown to react with intracellular thiols causing tumor growth suppression. Using these analogues as a template, two new compounds have been designed that feature a novel α-methylene indanone structural framework. Since ketones are better electrophiles than esters, it is hypothesized that these analogues will react more rapidly with thiols than their coumarin counterparts. The two α-methylene indanone analogues, one incorporating an isopropyl and the other an *n*-butyl substituent, have been prepared in five and seven steps respectively. Both synthetic sequences feature a 1,4-organometallic addition reaction, an intramolecular Friedel-Crafts acylation, and an alpha-methylenation of the key indanone intermediates.

Keywords: Cancer, Nuclear factor–kappa B, Glutathione, Coumarin, Indanone, Alpha-methylene

Introduction

Approximately 60 percent of all anti-cancer drugs used today are derived from natural products (1). Coumarin **[1]** is a natural product found in many plants (Figure 1). Recently, some simple coumarin analogues containing an α-methylene functional group were synthesized and shown to exhibit potent cytotoxicity against cancer (2). Analogues **[2]** and **[3]** both displayed IC_{50} values in the low micromolar range against leukemia, breast, and colon cancer cell lines (Figure 1).

The bioactivity of coumarin analogues **[2]** and **[3]** is thought to arise from the exocyclic methylene functional group found in their structures (2). Compounds that contain α-methylene lactones have been shown to be strong Michael acceptors, allowing them to react rapidly with intracellular thiols (3,4). By forming covalent, thioether bonds with cysteine amino acid residues, these compounds can both initiate apoptosis in cancer cells and inhibit unregulated cell growth. For example, glutathione (GSH) is a natural antioxidant found in all cells. Glutathione neutralizes free radicals, therefore protecting cells from oxidative stress. Natural products containing α,β-unsaturated carbonyls have been shown to react with GSH through a 1,4-addition reaction. By forming a thioether bond with the cysteine amino acid found in GSH, these compounds deplete GSH levels within the cell (5,6). This decrease in GSH leads to a redox imbalance which initiates apoptosis.

Compounds containing α-methylene lactones can also suppress tumor growth by inhibiting the nuclear factor-kappa B (NF-κB) pathway. NF-κB is a protein complex that controls DNA transcription during cell division. Over-activation of NF-κB has been found in a wide variety of tumor types (7). One method to prevent the activation of NF-κB is through inhibition of a kinase enzyme, IKK. The phosphorylation of two serine amino acid residues on IKK, Ser-177 and Ser-181, initiates the NF-κB activation sequence (8). Thiol-reactive agents, such as α-methylene lactones, can inhibit IKK by reacting with a cysteine amino acid residue, Cys-179, located between the two serines (9-13). Due to sterics, this thioether bond prevents IKK from being phosphorylated and therefore inhibits NF-κB activation and unregulated cell growth.

GSH depletion and NF-κB inhibition are two examples that illustrate the bioactivity of coumarin analogues **[2]** and **[3]** is highly dependent on their ability to react with thiols. Using this knowledge and the coumarin analogues as templates, two novel α-methylene 1-indanones, compounds **[5]** and **[6]**, were designed and synthesized (Figure 2). It is anticipated that these compounds will be more bioactive than their coumarin counterparts. The difference between these two indanone structures and the coumarin analogues is that a coumarin (compound **[1]**, Figure 1) contains an ester functional group while an indanone (compound **[4]**, Figure 2) contains a ketone. Ketones are better electrophiles than esters. It is therefore hypothesized that an α-methylene ketone will be more reactive than an α-methylene ester. Indanone analogues **[5]** and **[6]** should react more rapidly with intracellular thiols than coumarin analogues **[2]** and **[3]**. This increased reactivity should make them more cytotoxic. In addition, it is believed that indanone analogues **[5]** and **[6]** will have increased metabolic stability. Carboxylic esters can be cleaved in the body by enzymes called esterases (14). Once cleaved, the resulting metabolites can be excreted. Since the indanone analogues do not contain an ester, they should be more stable than the coumarins, therefore providing them more time to react with intracellular thiols.

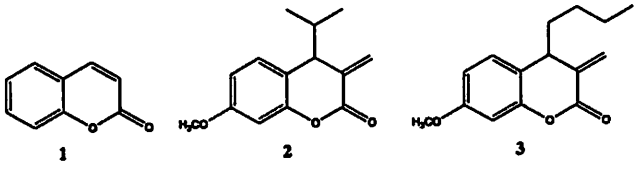


Figure 1. Coumarin [1] and α-Methylene Coumarin Analogues [2] and [3].

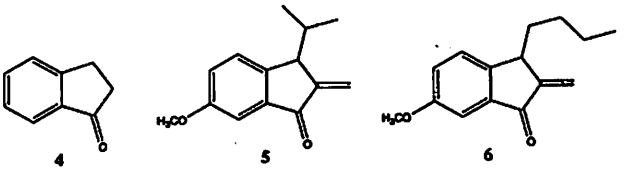


Figure 2. 1-Indanone [4] and α-Methylene Indanone Analogues [5] and [6].

Experimental

Column chromatography was performed on 230-400 mesh silica gel. NMR spectroscopy was recorded on a JEOL 400 MHz NMR spectrometer using deuterated chloroform solvent. Gas chromatography-mass spectrometry was carried out on an Agilent Technologies 7890/5975C gas chromatograph-mass spectrometer. The GC column (30m x 0.25mm) has a 0.25 μm thick polydimethyl-siloxane (PDMS) with 5% phenyl substitution stationary phase. The oven conditions were: injection port temperature = 250°C; oven starting temperature = 70°C for 5 minutes; ramp of 20°C/minute up to 250°C; the temperature was held for 10 minutes at 250°C. All starting chemicals were purchased from Sigma-Aldrich, Inc. (Atlanta, GA) and used as received.

Synthesis of Isopropyl Indanone Analogue **[5]**

Step 1A: 1,4-Addition of Grignard Reagent (15)

Commercially available 4-methoxycinnamic acid **[7]** (1.000 g, 5.612 mmol) was dissolved in tetrahydrofuran (35 mL). Isopropylmagnesium chloride (9.40 mL, 2.0 M in diethyl ether, 18.8 mmol) was added dropwise at room temperature and then the reaction was heated at reflux for 24 hours. The resulting mixture was cooled to room temperature and quenched with approximately 20 mL of 1.0 M HCl. An extraction with diethyl ether (2 x 50 mL) was performed and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (30% ethyl acetate in hexanes) to provide carboxylic acid **[8]** as a light yellow solid (0.887 g, 71.2%). **^{1}H NMR** (400 MHz) δ 7.05 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 2.87 – 2.80 (m, 1H), 2.77 (dd, J = 15.6, 5.6 Hz, 1H), 2.57 (dd, J = 15.6, 9.6 Hz, 1H), 1.87-1.76 (m, 1H), 0.92 (d, J = 7.2 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (400 MHz) δ 179.3, 158.1, 134.6, 129.2(2C), 113.6(2C), 55.2, 47.7, 38.5, 33.2, 20.7, 20.1. **GC-MS** RT = 12.745 min, M^+ = 222.

Steps 2A and 3A: Acyl Halide Preparation and Intramolecular Friedel-Crafts Acylation (16)

Carboxylic acid **[8]** (0.864 g, 3.89 mmol) was dissolved in dichloromethane (30 mL) and treated with thionyl chloride (0.70 mL, 9.60 mmol). The reaction mixture was stirred for two hours at room temperature. Aluminum chloride (0.778 g, 5.83 mmol) was added and the resulting mixture was stirred for 20 hours. The reaction was diluted with water (50 mL) and a dichloromethane extraction was performed (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (50% ethyl acetate in hexanes) to afford indanone **[9]** as a yellow oil (0.599 g, 75.4% over the two steps). **^{1}H NMR** (400 MHz) δ 7.24 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.4, 2.8 Hz, 1H), 7.02 (d, J = 2.8 Hz, 1H), 3.68 (s, 3H), 3.22-3.16 (m, 1H), 2.52 (dd, J = 19.2, 7.6 Hz, 1H), 2.31 (dd, J = 19.2, 2.8 Hz, 1H), 2.13-2.00 (m, 1H), 0.85 (d, J = 6.8 Hz, 3H), 0.53 (d, J = 7.2 Hz, 3H). **^{13}C NMR** (400 MHz) δ 206.4, 159.4, 150.5, 138.6, 126.6, 123.7, 104.6, 55.5, 43.5, 39.2, 31.4, 20.9, 16.6. **GC-MS** RT = 12.624 min, M^+ = 204.

Steps 4A and 5A: Alpha-Methylene Formation (4)

A 1.5 M sodium ethoxide solution was prepared by dissolving sodium metal (0.246 g, 10.7 mmol) in 7.1 mL of absolute ethanol. A cannula was used to transport the sodium ethoxide solution into a round bottom flask containing indanone **[9]** (0.540 g, 2.65 mmol). The resulting red solution was treated with diethyl oxalate (0.75 mL, 5.5 mmol) and allowed to stir at room temperature. After 24 hours, the reaction mixture was concentrated under vacuum to provide a dark red foam. The foam was dissolved in water (20 mL) and diethyl ether (10 mL) and poured into a separatory funnel. The flask was rinsed twice with 20 mL of water and 10 mL of diethyl ether to ensure complete transfer. An extraction was performed. The aqueous layer was collected and the diethyl ether layer was washed two more times with 20 mL portions of water. Intermediate **[10]**, currently in the form of a salt, was in the water layer. The combined aqueous layers were acidified with 1.0 M HCl. The acidic aqueous solution was subsequently extracted with dichloromethane (2 x 75 mL). The combined dichloromethane layers were dried over magnesium sulfate, filtered, and concentrated under vacuum to provide crude intermediate **[10]** as a red oil (0.688 g, 2.26 mmol). Intermediate **[10]** was characterized by GC-MS and carried on crude into the next step. **GC-MS** RT = 15.548 min, M^+ = 304.

Intermediate **[10]** (0.688 g, 2.26 mmol) was dissolved in 1,4-dioxane (5.0 mL) and treated with sodium acetate (0.005 g, 0.06 mmol), aqueous formaldehyde solution (1.0 mL, 37 wt. % in water, 13.4 mmol), and diethylamine (0.60 mL, 5.8 mmol). The resulting solution was stirred at room temperature. After 48 hours, the reaction mixture was acidified to a pH of 1 with 1.0 M HCl. An ethyl acetate extraction was performed (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford crude product **[5]**. The crude product was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford alpha-methylene indanone **[5]** as an orange oil (0.438 g, 76.6% over the two steps). **^{1}H NMR** (400 MHz) δ 7.31 (d, J = 8.4 Hz, 1H), 7.19 (d, J = 2.8 Hz, 1H), 7.11 (dd, J = 8.0, 2.8 Hz, 1H), 6.24 (dd, J = 2.0, 0.8 Hz, 1H), 5.49 (dd, J = 1.6, 0.8 Hz, 1H), 3.76 (s, 3H), 3.66-3.63 (m, 1H), 2.22-2.10 (m, 1H), 0.80 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H). **^{13}C NMR** (400 MHz) δ 193.8, 159.6, 147.4, 145.8, 139.4, 126.8, 124.1, 118.8, 105.5, 55.6, 47.9, 33.3, 19.6, 18.5. **GC-MS** RT = 13.035 min, M^+ = 216.

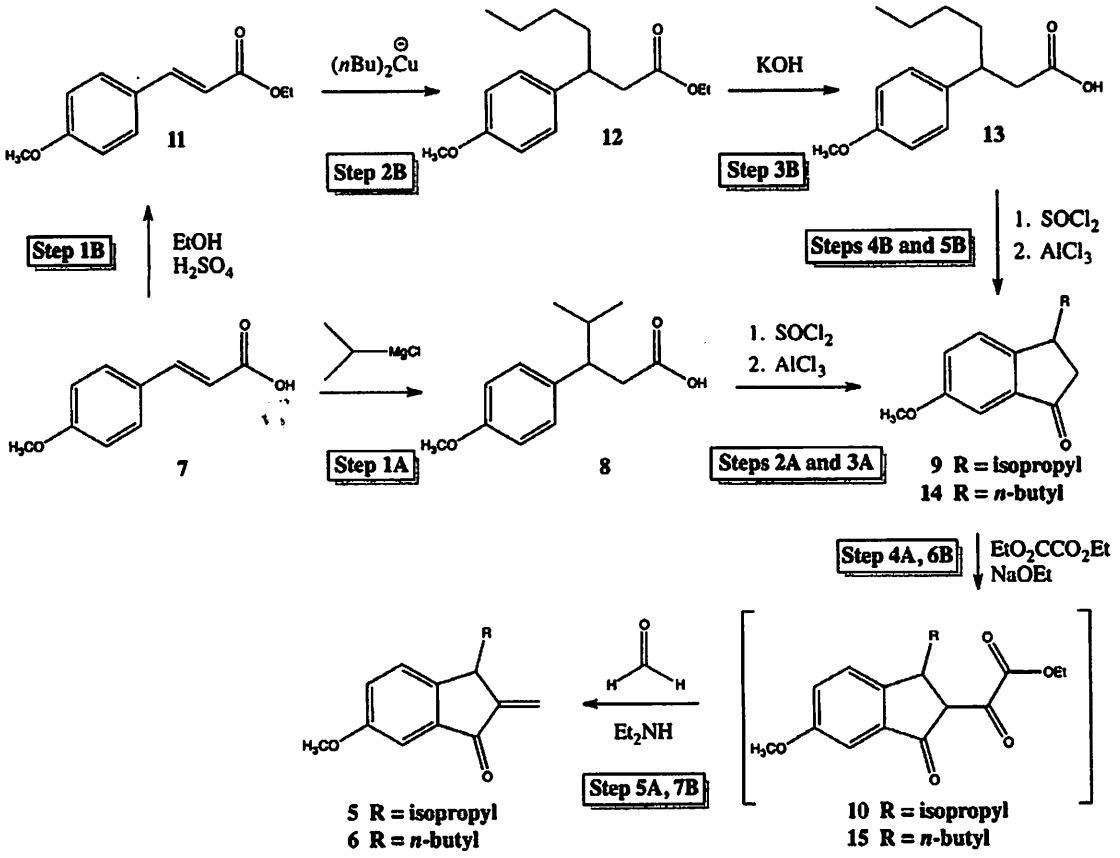
Synthesis of n-Butyl Indanone Analogue **[6]**

Step 1B: Fischer Esterification

Commercially available 4-methoxycinnamic acid **[7]** (1.000 g, 5.612 mmol) was dissolved in absolute ethanol (10 mL). The resulting solution was treated with concentrated sulfuric acid (1.0 mL, 18 mmol) and heated at reflux for 5 hours. The reaction was quenched with 10% sodium carbonate(aq) until a pH of 8 was achieved. A diethyl ether extraction (2 x 60 mL) was performed and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide carboxylic ester **[11]** as a white solid (1.128 g, 97.57%). **^{1}H NMR** (400 MHz) δ 7.62 (d, J = 16.0 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.29 (d, J = 16.0 Hz, 1H), 4.23 (q, J = 6.8 Hz, 2H), 3.81 (s, 3H), 1.31 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (400 MHz) δ 167.4, 161.4, 144.3, 129.8(2C), 127.3, 115.8, 114.4(2C), 60.4, 55.4, 14.4. **GC-MS** RT = 12.751 min, M^+ = 206.

Step 2B: 1,4-Addition of Dialkylcuprate (17)

Copper(I) iodide (1.034 g, 5.430 mmol) was dissolved in anhydrous diethyl ether (15 mL) and placed in a -40°C acetone



Scheme 1. Synthesis of Indanone Analogues [5] and [6].

bath (the temperature was maintained using a cryocooler). Commercially available butylmagnesium chloride solution (5.40 mL of a 2.0 M solution in THF, 10.8 mmol) was added to the copper (I) iodide and the resulting suspension was stirred at -40°C for 4 hours. A separate round bottom flask containing ester **[11]** (0.534 g, 2.59 mmol) dissolved in anhydrous diethyl ether (15 mL) was subsequently added via cannula to the organocuprate. The acetone bath temperature was warmed to -20°C and the reaction was allowed to stir for 2.5 hours. At -20°C, the reaction was quenched with saturated ammonium chloride(aq) (20 mL). A diethyl ether extraction was performed (3 x 50 mL) and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide ester **[12]** as a light yellow oil (0.673 g, 98.4%). **^{1}H NMR** (400 MHz) δ 7.08 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 4.00 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.08-2.97 (m, 1H), 2.57 (dd, J = 14.6, 6.8 Hz, 1H), 2.49 (dd, J = 14.6, 8.0 Hz, 1H), 1.68-1.48 (m, 2H), 1.33-1.08 (m, 4H), 1.11 (t, J = 7.2 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (400 MHz) δ 172.6, 158.1, 136.3, 128.4(2C), 113.8(2C), 60.2, 55.2, 42.2, 41.5, 36.1, 29.6, 22.6, 14.2, 14.0. **GC-MS** RT = 13.234 min, M^+ = 264.

Step 3B: Saponification

Carboxylic ester **[12]** (0.673 g, 2.55 mmol) was treated with 3.0 M KOH(aq) (10.0 mL, 30.0 mmol) and heated to reflux. The mixture was allowed to stir for 3 hours. An extraction was performed using 1.0 M KOH (30 mL) and diethyl ether (30 mL). The diethyl ether layer was washed a second time with 1.0 M KOH (30 mL). The combined aqueous layers were acidified with concentrated HCl until a pH of 1 was achieved. A second extraction was then performed on the acidic aqueous layer using diethyl ether (2 x 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford pure carboxylic acid **[13]** as a yellow oil (0.551 g, 91.6%). **^{1}H NMR** (400 MHz) δ 11.4-11.1 (br s, 1H), 7.10 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 3.78 (s, 3H), 3.08-2.97 (m, 1H), 2.63 (dd, J = 15.2, 7.2 Hz, 1H), 2.56 (dd, J = 15.6, 8.0 Hz, 1H), 1.72-1.50 (m, 2H), 1.36-1.05 (m, 4H), 0.83 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (400 MHz) δ 179.1, 158.2, 136.1, 128.4(2C), 113.9(2C), 55.2, 41.9, 41.1, 36.2, 29.6, 22.6, 14.1. **GC-MS** RT = 13.313 min, M^+ = 236.

Steps 4B and 5B: Acyl Halide Preparation and Intramolecular Friedel-Crafts Acylation (16)

The same procedure was used as described for Steps 2A and 3A. Carboxylic acid **[13]** (0.551 g, 2.33 mmol) was treated with thionyl chloride followed by aluminum chloride. The resulting crude product was purified by column chromatography (50% ethyl acetate in hexanes) to provide indanone **[14]** as a light yellow oil (0.247 g, 48.5% over the two steps). **^{1}H NMR** (400 MHz) δ 7.33 (d, J = 8.4 Hz, 1H), 7.12 (dd, J = 8.0, 2.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 3.76 (s, 3H), 3.25-3.18 (m, 1H), 2.80 (dd, J = 19.2, 7.2 Hz, 1H), 2.30 (dd, J = 19.2, 3.2 Hz, 1H), 1.87-1.77 (m, 1H), 1.45-1.19 (m, 5H), 0.85 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (400 MHz) δ 206.4, 159.5, 151.9, 137.9, 126.4, 123.9, 104.7, 55.6, 43.8, 37.6, 36.0, 29.8, 22.8, 14.1. **GC-MS** RT = 13.367 min, M^+ = 218.

Steps 6B and 7B: Alpha-Methylene Formation (4)

The same procedure was used as described for Steps 4A and 5A. Indanone **[14]** (0.140 g, 0.642 mmol) was treated with sodium ethoxide and diethyl oxalate. The ethyloxalyl

product **[15]** was characterized by GC-MS and carried on crude into the next step. **GC-MS** RT = 16.424 min, M^+ = 318.

Intermediate **[15]** was treated with sodium acetate, aqueous formaldehyde, and diethylamine. The resulting product was purified by column chromatography (50% ethyl acetate in hexanes) to afford alpha-methylene indanone **[6]** as a yellowish-orange oil (0.0887 g, 60.1% over the two steps). **^{1}H NMR** (400 MHz) δ 7.37 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 2.8 Hz, 1H), 7.18 (dd, J = 8.6, 2.8 Hz, 1H), 6.31 (d, J = 2.0 Hz, 1H), 5.55 (d, 0.8 Hz, 1H), 3.83 (s, 3H), 3.81-3.76 (m, 1H), 1.87-1.77 (m, 2H), 1.31-1.03 (m, 4H), 0.82 (t, J = 6.8 Hz, 3H). **^{13}C NMR** (400 MHz) δ 193.7, 159.6, 148.8, 147.1, 139.0, 126.4, 124.5, 118.5, 105.5, 55.7, 41.6, 34.6, 27.8, 23.0, 14.0. **GC-MS** RT = 13.700 min, M^+ = 230.

Results and Discussion

Preparation of isopropyl α-methylene indanone analogue **[5]** proceeded as expected. Addition of isopropylmagnesium chloride to commercially available 4-methoxycinnamic acid **[7]** provided the 1,4-addition product **[8]** as reported in the literature (15). Some 1,2-addition product was observed by GC-MS analysis (80% 1,4-addition: 20% 1,2-addition). The 1,2-addition product, (*E*)-3-isopropyl-1-(4-methoxyphenyl)-4-methyl-1-penten-3-ol, was easily removed by column chromatography. Addition of thionyl chloride to the 1,4-addition product **[8]** afforded the acyl halide which upon treatment with aluminum chloride performed an intramolecular Friedel-Crafts acylation reaction to provide the desired indanone intermediate **[9]** in a 53.7% yield over the three steps (16). A previously reported, two-step α-methylenation process was used to complete the synthesis of α-methylene indanone analogue **[5]** (4). The enolate anion of indanone **[9]** was treated with diethyl oxalate to form ethyloxalyl derivative **[10]** which was characterized by GC-MS. Upon treatment with aqueous formaldehyde and diethylamine, crude intermediate **[10]** performed a Mannich-type reaction followed by a β-dicarbonyl cleavage to afford α-methylene indanone **[5]** in a 76.6% yield over the two steps (4,18).

Complications with the synthesis arose when the same sequence was attempted with an *n*-butyl Grignard reagent. Treatment of 4-methoxycinnamic acid **[7]** with butylmagnesium chloride did not provide the desired 1,4-addition product. The major product observed was (*E*)-3-butyl-1-(4-methoxyphenyl)-1-hepten-3-ol made from 1,2-addition of the Grignard reagent to the carboxylic acid (69% based on GC-MS analysis). After reading the literature, it was discovered that only bulky nucleophiles, like isopropyl and *tert*-butyl Grignard reagents, provide the desired 1,4-addition products when added to 4-methoxycinnamic acid **[7]** (15). To circumvent this problem, the carboxylic ester **[11]** was prepared via a Fischer esterification reaction. Ester **[11]** was then treated with a dialkylcuprate generated from butylmagnesium chloride addition to copper(I) iodide (17). This reaction led to almost exclusive formation of the desired 1,4-addition product **[12]** (95% based on GC-MS analysis). The alkylated ester **[12]** was then converted back into a carboxylic acid and the same synthetic steps as used for isopropyl analogue **[5]** were used to transform carboxylic acid **[13]** into the desired α-methylene indanone **[6]** (4,16).

Conclusion

The isopropyl, α-methylene indanone analogue **[5]** was prepared in five steps in a 41.1% overall yield (83.7% yield per step). The α-methylene, *n*-butyl indanone analogue **[6]** was synthesized in seven steps in a 25.6% overall yield (82.3% yield per step). While similar α-methylene indanone structures have been prepared via palladium-catalyzed cyclocarbonylation reactions, the two synthetic methodologies reported in this publication allow for a much simpler route to this class of compounds (19). It is anticipated that indanone analogues **[5]** and **[6]** will be more bioactive and have a greater metabolic stability than their corresponding coumarin derivatives.

Acknowledgment

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