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Synthesis of 1-[$^{13}CD_3$]-9-*cis*-Retinoic Acid

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Summary

1-[$^{13}CD_3$]-9-*cis*-Retinoic acid was prepared in 8 steps from 2,6-dimethylcyclohexanone. Alkylation of 2,6-dimethylcyclohexanone under LiHMDS/$MnBr_2$/$^{13}CD_3I$ gave the corresponding labeled 2-[$^{13}CD_3$]-2,2,6-trimethylcyclohexanone **4** in good yield. Further functionalization of **4** to 6-[$^{13}CD_3$]-β-cyclocitral **6** proceeded through a Shapiro reaction. Aldehyde **6** was condensed with ethyl 3,3-dimethylacrylate to afford the corresponding bicyclic pyranone **7**. Reduction of **7** to lactol **8**, followed by acid-catalyzed ring opening gave the 9-*cis*-aldehyde **9**. Wittig-Horner olefination and saponification afforded the title compound in good overall yield and in excellent isotopic purity.

Key Words: 2-[$^{13}CD_3$]-2,2,6-trimethylcyclohexanone, 6-[$^{13}CD_3$]-β-cyclocitral and 1-[$^{13}CD_3$]-9-*cis*-retinoic acid

Introduction

Retinoids have been shown to be effective agents for the treatment of dermatological diseases, and more recently, for the control of a variety of cancers in laboratory animals and in man (1). Accordingly, all-*trans* retinoic acid (ATRA) **1** (Figure), 13-*cis*-retinoic acid (13-*cis*-RA) and Etretinate®, an aromatic tetraenic ethyl ester, are currently in clinical trials for evaluation as potential anticancer agents (2). Retinoids exert their anticancer effects by inhibiting cellular proliferation and inducing differentiation of cells through the modulation of intracellular receptors, which results in the alteration of gene expression. Two distinct classes of retinoid receptors have been identified; the retinoic acid receptors (RARα,β,γ) and the retinoid X receptors (RXRα,β,γ) (3).

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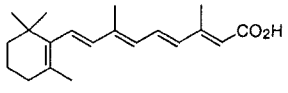
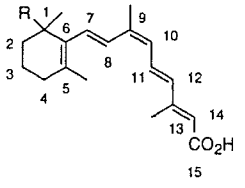
The recent identification of 9-*cis*-retinoic acid (9-*cis*-RA, Figure) **2a** as an endogenous hormone that binds and activates both classes of retinoid receptors has generated interest in the mode of action of this novel hormone and its potential for the treatment of proliferative diseases (4). Advancement of 9-*cis*-retinoic acid to clinical evaluation necessitated the generation of isotopically labeled derivatives in order to investigate the bioavailability, stability and metabolism of this natural hormone (5). In addition, it was desirable to prepare a 9-*cis*-RA derivative having the label at one of the least oxidizable positions in the cyclohexene ring. Herein we report an efficient synthesis of highly pure 1-[$^{13}CD_3$]-9-*cis*-RA **2b** which presented us several challenges including the introduction of the label in a highly efficient manner, the installation and preservation of the 9-*cis* double bond and the preparation of the title compound in gram scale quantities. Many ^{13}C-labeled retinal and all-*trans*-retinoic acid were previously prepared (6). However no synthesis of 9-*cis*-RA containing labels at the 1-position were reported.

Figure 1



all-trans-Retinoic Acid (ATRA) **1**



9-cis-Retinoic Acid (*9-cis*-RA) **2a** (R=CH_3)

1-[$^{13}CD_3$]-*9-cis*-Retinoic Acid **2b** (R=$^{13}CD_3$)

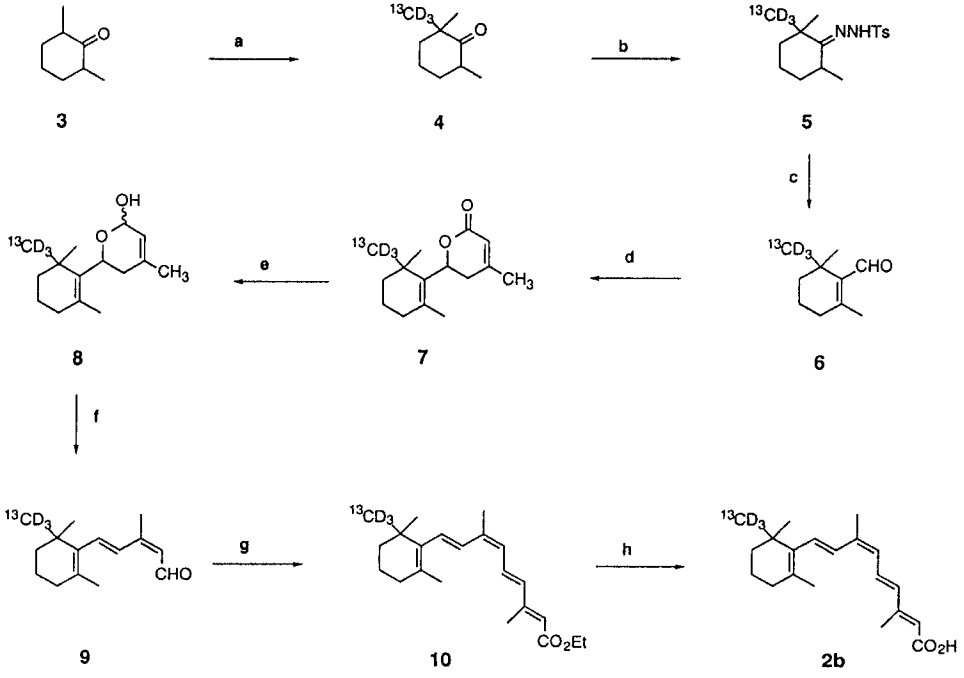
* *The traditional retinoid numbering system is being used*

Our synthetic scheme relies on the labeling of 2,6-dimethylcyclohexanone with $^{13}CD_3I$. Although α-alkylation of ketones is one of the standard reactions in organic synthesis (7), the preparation of α-keto tertiary centers is usually plagued by the undesired formation of poly-*C*- and *O*-alkylated products (10-30%) and the necessary use of a large excess of the primary alkylating reagent which in the case of labeled reagents, would be inefficient and relatively costly (8). Recently, Reetz and Haning reported that transmetallation of cyclic ketones lithium enolates using $MnBr_2$ generates manganese-enolates which react with *one equivalent* of CH_3I to provide α-methylated ketones without the formation of polyalkylated by-products (9). This timely report prompted us to carry out the labeling of 2,6-dimethylcyclohexanone **3** under LiHMDS/$MnBr_2$/$^{13}CD_3I$ conditions, which indeed proceeded, on a 0.25 mole scale, to give 2-[$^{13}CD_3$]-2,2,6-trimethylcyclohexanone **4** in 83% yield (94% chemical purity by GC and >98%

isotopic purity, Scheme). Labeled 2,2,6-trimethylcyclohexanone **4** was converted to the corresponding *p*-toluenesulfonyl hydrazone **5** in ethanol (46% yield; 45% of the starting ketone was recovered) which was sequentially treated with *n*-BuLi-TMEDA-hexanes (-78°C to RT) and dimethylformamide to give 6-($^{13}CD_3$)-β-cyclocitral **6** in 68% yield after chromatography (10). Treatment of labeled β-cyclocitral **6** with the lithium anion derived from ethyl 3,3-dimethylacrylate gave lactone **7** in 43% yield, along with the corresponding ω-hydroxy ester (46%) which was easily separated from **7** by chromatography (11).

The crucial introduction of the 9-*cis* double bond was efficiently performed as follows: Dibal reduction of **7** gave in nearly quantitative yield lactol **8** which was transformed to the 9-*cis* aldehyde **9** upon treatment with HCl in dichloroethane (12). Chain homologation of **9** using diethyl 3-ethoxycarbonyl-2-methylprop-2-enyl phosphonate in THF/DMPU at –78°C afforded ester **10** in 78% yield (~15:1 (13-E/Z) ratio by ^1H NMR). Saponification of ester **10** gave the desired 1-[$^{13}CD_3$]-9-*cis*-RA **2b**, which after two consecutive recrystallizations from EtOH:H_2O was >99% pure (HPLC, HRMS Fab, NMR, IR and UV).

Scheme



a. LiHMDS, THF, DMPU, $MnBr_2$, $^{13}CD_3I$, (83%); b. *p*-$TsNHNH_2$, HCl, EtOH (46%); c. i. n-BuLi, TMEDA, Hexanes, -78°C–RT; ii. DMF (68%); d. LDA, Ethyl 3,3-dimethylacylate (43%); e. Dibal, THF (99%); f. HCl-DCE, (89%); g. *n*-BuLi, $(EtO)_2P(O)CH_2C(CH_3)=CHCO_2Et$, DMPU, THF (78%); h. NaOH, EtOH (78%)

In summary, we have developed a highly efficient eight-step synthesis of 1-[$^{13}CD_3$]-9-*cis*-RA **2b** starting from readily available 2,6-dimethylcyclohexanone. This material will be useful in studying the metabolic profile of this new endogenous hormone.

Experimental Section

The organic solvents were purchased from Fisher Scientific, THF was distilled from Na (metal) in the presence of benzophenone. Thin layer chromatography was performed on Merck Kieselgel 60 F-254 plates. ^1H and ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer (protons are assigned in ppm according to the accepted retinoid numbering system as shown in Figure 1). UV spectra were measured on a Kontron Uvikon Model 941 Spectrometer, and HPLC analysis was performed on a Waters system using a Beckman C18 Ultrasphere column.

[(*R,S*)-2-[$^{13}CD_3$]]-2,2,6-Trimethylcyclohexanone 4

To a flame dried 2 L three neck round bottom flask equipped with a dry solid-addition funnel and a 500 mL addition funnel, THF (200 mL) and lithium hexamethyldisilazide (535 mL of a 1 M solution in THF; 0.535 mol) were added and the mixture was cooled to –78°C. 2,6-Dimethyl cyclohexanone **3** (30.0 g; 32.43 mL; 0.237 mol) was slowly added. The mixture was stirred at –78°C for 60 min, then warmed to room temperature. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H) pyrimidinone (DMPU) (90 mL; 0.71 mol) was added and the mixture stirred at 23°C for 20 min. Solid, pre-dried anhydrous $MnBr_2$ (24 h. in the presence of P_2O_5 under high vaccum (~ 0.1 torr.)), was slowly added over 20 min. as the solution turned to a dark red. Stirring was continued for 30 min., [$^{13}CD_3$]-methyl iodide (37.2 g, 0.26 mol) was slowly added, and the mixture was stirred at room temperature for 4 hours. The mixture was carefully quenched with a sat. NH_4Cl solution (250 mL). Diethyl ether (500 mL) was added and the organic layer was separated, washed with an aqueous EDTA solution (3 x 250 mL), a sat. solution of $NaHCO_3$ (2 x 250 mL), a sat. solution of $CuSO_4$ (2 x 250 mL), water (2 x 100 mL), brine (2 x 100 mL) and dried over $MgSO_4$. The solvents were evaporated and the residue was distilled. The fraction that boiled at 95-97°C at 53-57 mbar gave 28.0 g of the desired ketone. GC analysis showed a 94% pure sample. Impurities included a mixture of starting ketone (4%), and O-methylated compound in ~2%; IR (neat) 2968, 2931, 2870, 1707, 1456, 1385, 1126 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz): δ 2.54 (m, 1H), 2.1-1.2 (mm, 6 H, CH-ring), 1.09 (d, J = 4.7 Hz, CH-C<u>H</u>3, major diastereomer), 1.15 (d, J = 4.9 Hz, CH-C<u>H</u>3, minor diastereomer), 0.94 (d, J = 4.6 Hz, gem-CH_3, minor diastereomer), 0.9 (d, J = 6.5 Hz, gem-C<u>H</u>3, major diastereomer); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 217.0, 45.2, 41.6, 40.6, 36.6, 25.4, 24.9 (2 x hept.), 21.4, 14.8; HRMS for $C_8H_{13}O(^{13}CD_3)$ calcd: 145.1501, found: 145.0867.

(*R,S*)-6-[$^{13}CD_3$]-2,6,6-Trimethylcyclohexyl *p*-toluenesulfonyl hydrazone **5**

A suspension of *p*-toluenesulfonylhydrazide (21.13 g, 0.127 mol) in absolute ethanol (30.0 mL) containing conc. HCl (1.0 mL) was heated to 80°C for 2 min., then allowed to cool to ~35°C. (*R,S*)-2-[$^{13}CD_3$]-2,2,6-trimethylcyclohexanone **4** (16.44 g, 0.127 mol) was added, and the mixture was heated at 82°C for 4 h. The mixture was cooled to room temperature and the solvents evaporated. The crude residue was purified by silica gel chromatography to give the starting ketone (7.5 g) and the desired hydrazone (18.38 g, 46% yield). The hydrazone was recrystallized from a mixture of EtOAc: pentane (1:20) to give white crystals (17.75 g); IR (neat) 3223, 2931, 2200, 2100-1800, 1599, 1400 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 7.84 (d, J = 8.2 Hz, 2 H, *Ar-H*), 7.63 (s, 1 H, NH), 7.29 (d, J = 8.2 Hz, 2 H, *Ar-H*), 2.75 (m, 1 H), 2.42 (s, 3 H, Ar-CH_3)1.8-1.25 (m, 6 H, CH-ring), 1.08 (d, J = 4.7 Hz, gem-CH_3), 1.05 (d, J = 7.45 Hz, CH-CH_3), the chemical shifts of the second diastereomer are essencially the same with the exception of δ 0.99 (d, J = 4.7 Hz, gem-CH_3); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 167.9, 143.7, 135.4, 129.2, 128.0, 39.7, 38.0 (d), 31.3, 29.1, 28.1 (hept.), 27.35, 21.5, 17.7, 16.7; HRMS for $C_{15}H_{20}N_2OS$ ($^{13}CD_3$) calcd: 313.1859, found: 313.1857.

(*R,S*)-6-[$^{13}CD_3$]-2,6,6-Trimethyl-1-cyclohexene-1-aldehyde **6**

A 100 mL three-neck, round-bottom flask, fitted with a solid addition funnel, was flame-dried under nitrogen, then charged with anhydrous TMEDA (15.0 mL) and *n*-BuLi (13.9 mL of a 2.5 M solution in hexanes; 34.4 mmol). The mixture was cooled to –78°C and hydrazone **5** (3.0 g, 9.61 mmol) was added. The reaction mixture was stirred at –78°C for 30 min. then allowed to warm to room temperature and stirred for 4 h. The mixture was cooled to -78°C, DMF (1.6 mL) was added and the mixture was warmed to room temperature. After 12 h., water (20 mL) was slowly added and the mixture extracted with ether (3x 30 mL). The organic layer was washed with sat. $CuSO_4$ (2 x 10 mL), water (20 ml), brine (20 mL) and dried over $MgSO_4$. The solvents were evaporated to afford a yellow residue which was purified by silica gel chromatography (sgc) to give 1.03 g (68% yield) of ring labeled β-cyclocitral as a clear liquid: IR (neat) 2933, 2870, 1718, 1672, 1612, 1456, 1417, 1373, 1300 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz): δ 10.10, (s, 1H, -CHO), 2.16 (t, J = 6.1 Hz, 2 H,-CH_2-), 2.06 (s, 3 H), 1.58 (m, 2 H), 1.42 (m, 2 H), 1.16 (d, J = 4.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$; 100 MHz): δ 192.14, 156.0, 140.55, 20.3, 35.6, 27.6, 27.2 (hept.), 26.4, 22.6, 19.2; HRMS for $C_9H_{13}O(^{13}CD_3)$ calcd: 156.1423, found: 156.1593.

(*R,S*)-5,6-Dihydro-4-methyl-6-[6-[$^{13}CD_3$]-2,6,6-trimethylcyclohex-1-en-1-yl]-2H pyran-2-one **7**

A flame-dried 500 mL round bottom flask was charged with tetrahydrofuran (THF) (100 mL) and anhydrous diisopropyl amine (distilled over CaH_2) (2.65 mL, 19.0 mmol), was added and the mixturewas cooled to –20°C. A solution of *n*-BuLi in hexanes (7.35 mL of a 2.35 M solution; 18.2 mmol) was added over a 10 min. period. The solution was stirred at –20°C for 15 min then cooled to –78°C. To the above solution was added ethyl dimethylacrylate (Aldrich Inc.) (1.92 g, 15 mmol) in THF (5.0 mL) at such a rate that the internal temperature did not go higher than –73°C. The mixture was stirred at –78°C for 30 min., after which a precooled (–78°C) solution of aldehyde **6** (2.23 g, 14.29 mmol) in THF (25 mL) was added dropwise. When the addition was complete, the reaction mixture was immediately allowed to warm to 0°C and quenched at 0°C with a saturated sodium bicarbonate solution (3.0 mL). The mixture was stirred at room temperature for 60 min., followed by the addition of water (10 mL) and extraction with EtOAc (2x 50 mL). The organic layer was washed with brine (2 x 10 mL), dried over $MgSO_4$ and concentrated. The residue was purified by sgc using a mixture of hexanes:EtOAc 5:1 as eluent to give 1.53 g of the desired lactone, 43% yield; mp. 77-79°C; IR (neat) 2958 (CH aliph.), 1720 (C=O), 1383 (C=C), 1294, 1251 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 5.82 (s, 1 H, CH-C(O)O–), 5.50 (m, 1 H, vinyl-CH), 4.95 (dd, J = 13.3, 4.4 Hz, 1 H, –CH–O-C(O)), 2.82 (m, 1H, -CH-CH -O-, syn), 2.12 (dd, J = 16.3, 4.4 Hz, 1 H, -CH-CH -O-, anti), 1.97 (s, 3 H, CH_3-ring), 1.74 (s, 3 H, CH_3 ring),1.6-1.3 (m, 4 H, ring), 1.07 (d, J = 4.8 Hz, 3 H, CH_3-ring, one diastereomer), 0.95 (d, J = 4.8 Hz, 3 H, CH_3 ring, other diastereomer); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 165.8, 157.6, 135.9, 134.2, 75.6, 39.4, 35.3, 34.2 (d), 33.9, 28.61, 27.9 (hept, one diastereomer), 26.7 (hept, other diastereomer), 22.9, 21.4, 19.0; HRMS for $C_{14}H_{19}O_2(^{13}CD_3)$ calcd: 238.1842, found: 238.1832.

(*R,S*)-(2Z,4E)-3-Methyl-5-(-6-[$^{13}CD_3$]-2,6,6-trimethylcyclohex-1-en-1-yl)-2,4-pentadienenal **9**

A solution of pyran-2-one **7** (223 mg, 0.96 mmol) in THF (10.0 mL) was cooled at –78°C and a solution of diisobutylaluminum hydride in toluene (1.0 mL of a 1.0 M solution) was slowly added. The progress of the reaction was monitored by TLC (hexanes:EtOAc 4:1). After 15 min. the reaction was complete, a saturated solution of Rochelle salt (4.0 mL) was added at –78°C, followed by warming to room temperature. EtOAc (20 mL) was then added and the layers were separated. The aqueous layer was thoroughly extracted with EtOAc (3x 10 mL). The combined organic layers were washed with brine (20 mL) then concentrated to give 220 mg (98% yield) of virtually pure

desired lactol **8**. This compound, obtained as white solid mp. 146-148°C and as a single diastereomer, was directly taken through the next step without further analysis. A solution of lactol **8** (220 mg, 0.94 mmol) in 1,2-dichloroethane (DCE) (5.0 mL) was added to 10% HCl (5.0 mL), and the biphasic system was heated at 55°C with vigorous stirring. The reaction was monitored carefully by TLC and was complete after 60 min. The mixture was cooled to room temperature and neutralized using a saturated solution of $NaHCO_3$. The layers were separated and the aqueous phase extracted with dichloromethane (2 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL) and brine (10 mL), dried over $MgSO_4$ then concentrated. The residue was purified on a short sgc column to give 174 mg (86% yield) of the desired aldehyde as a yellow oil: IR (neat) 2958, 2928, 2866, 1668 (C=O), 1614 (C=C); ^1H NMR ($CDCl_3$; 400 MHz) δ 10.17 (d , J = 8.0 Hz, CHO), 7.08 (d , J = 16.0 Hz, vinyl-CH, trans), 6.63 (d, J = 16.0 Hz, vinyl-CH), 5.86 (d, J = 8.0 Hz, 1H, C<u>H</u>–CHO), 2.13 (s, 3 H, -C-(CH_3)=CH-CHO), 2.07 (m, 2 H), 1.751.62 (m, 2 H), 1.48 (m, 2 H),1.04 (d, J = 4.7 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 190.2, 155.2, 137.2, 136.5, 132.3, 127.8, 127.7, 39.4, 34.0 (d), 33.2, 28.8, 28.2 (hept), 21.8, 21.1, 19.0; HRMS for $C_{14}H_{19}O(^{13}CD_3)$ calcd: 222.1893, found: 222.1880.

<u>Ethyl *(R,S)*-(2E,4E,6Z,8E)-3,7-dimethyl-9-(6-[$^{13}CD_3$]-2,6,6-trimethylcyclohex-1-yl)-nonatetraenoate **10**</u>

A solution of diethyl 3-ethoxycarbonyl-2-methylprop-2-enylphosphonate (354 mg, 1.34 mmol) in anhydrous THF (5.0 mL) was cooled to 0°C, and treated with anhydrous DMPU (0.5 mL) and *n*-BuLi in hexanes (0.56 mL of a 2.35 M solution, 1.33 mmol). The mixture was stirred at 0°C for 20 min., then cooled to –78°C. A solution of triene aldehyde **9** (241 mg, 1.10 mmol) in THF (3.0 mL) was slowly added, and the reaction mixture was stirred at –78°C for an additional 60 min. The mixture was allowed to warm to 0°C to effect the completion of the reaction. A sat. solution of ammonium chloride (5 mL) was added and the mixture extracted using EtOAc (3x 10 mL). The combined organic extracts were washed with water (2 x 5 mL) and brine (10 mL), dried over $MgSO_4$ and then concentrated. The residue was purified on a short sgc column to give 296 mg (78% yield) of the desired ester in a ~15:1 ratio (13-E/Z isomers); IR (neat) 2928, 1709 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ (ppm) 7.08 (dd, J = 15, 11.3 Hz, 1 H), 6.65 (d, J = 16 Hz, 1 H), 6.29 (d, J = 15 Hz, 1 H), 6.23 (d, J = 15 Hz, 1 H), 6.06 (d, J = 11.3 Hz, 1 H), 5.6 (m, 1 H), 5.52 (m, 1 H), 4.17 (d, J=7 Hz, 2 H), 2.7 (s, 2 H), 2.33 (s, 3 H), 2.03 (s 3 H), 1.82 (s, 3 H) 1.29 (t, J = 7 Hz, 3 H), 1.05 (d, J = 4.8 Hz, 3 H); HRMS for $C_{21}H_{26}O(^{13}CD_3)$ calcd: 332.2640, found: 332.2641.

(*R,S*)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[6-[$^{13}CD_3$]-2,6,6-trimethylcyclohex-1-yl]-nonatetraenoic acid

A solution of ester **10** (748 mg, 2.24 mmol) in ethanol (20 mL) was treated with a NaOH solution (990 mg in 18.0 mL of water) and the mixture was heated for 1 hour at 70°C. The solution was cooled to room temperature, followed by addition of excess 10% HCl. The mixture was extracted with EtOAc (3 x 20 mL) and the organic layer was washed with water (3 x 5 mL), brine (3 x 5 mL), dried over $MgSO_4$, filtered, and evaporated to give a yellowish solid. The crude product was dissolved in 15.0 mL of hot ethanol followed by water (1.8 mL). The mixture was allowed to cool to room temperature. The solid material was filtered and the recrystallization repeated once to give the desired compound (535 mg, 78% yield), mp. 188-190°C; IR (KBr, cm^{-1}) 2914, 1670, 1583; ^1H NMR ($CDCl_3$; 400 MHz): d (ppm) 7.20 (dd, J = 15.0 Hz, 1 H), 6.65 (d, J = 16.0 Hz, 1 H), 6.28 (d, J = 16.0 Hz, 1 H), 6.25 (d, J =15.0 Hz, 1 H), 6.06 (d, J = 11.0 Hz, 1 H), 5.80 (s, 1 H), 2.35 (s, 3 H), 2.05 (t, J = 6.6 Hz, 2 H), 2.01 (s, 3 H), 1.75 (s, 3 H), 1.64 (m, 2 H), 1.49 (m, 2 H), 1.04 (d, J = 4.8 Hz, 3 H); UV (MeOH): λ max = 343 (37,800); MS m/e 305 (M+1), 259, 245, 217, 205, 199, 185.

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