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The preparation of ketone constituents from *Echinacea pallida*

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ABSTRACT

Efficient syntheses of two ketones from *Echinacea pallida* are described.

1. Introduction

Echinacea angustifolia, *Echinacea pallida*, and *Echinacea purpurea* are the main *Echinacea* species and have been used to treat infections and enhance the immune system.[1] *Echinacea* has ranked among the leading botanical supplements sold worldwide. In recent years, the treatment of rhinoviruses using *Echinacea* has been the focus of a number of studies, several of which have failed to show the efficacy of *Echinacea*.[2] Commercial *Echinacea* is often a mixture of species and there is no standardization of the chemical components. As part of a program designed to define the chemical fingerprint of *Echinacea* species as a necessary step toward standardization, we report herein the syntheses of two bioactive ketone components of *E. pallida*.[3]

As shown in Fig. 1, ketones **1**–**3** from *E. pallida* exhibit a range of biological activities.[4] Recently, Chicca and co-workers reported that **3** showed a concentration dependent cytotoxicity on several human cancer cell lines, including leukemia (Jurkat and HL-60), breast carcinoma (MCF-7), and melanoma (MeWo) cells.[5] Binns has reported that the ketones from *E. pallida* are potent antifungal agents.[6] Related acetylenic ketones have been reported by Bohlmann in *Centaurea ferox* roots.[7] Despite the potential value of the ketones from *E. pallida*, few reports of synthesis of authentic standards or analogs have been reported. Crombie and co-workers reported the first syntheses of related amides using organometallic coupling reactions.[8] Wailes has also reported the synthesis of related dienamides.[9] Kraus reported the synthesis of ketones **1**[10] and **2**.[11] Recently, Benvenuti and Prati reported a clever synthesis of **3**.[12]

Although we reported the first synthesis of **2**, the number of steps and low overall yield limited the amount of ketone that could be prepared for biological testing. We report herein a more efficient synthesis via a phosphonium salt route. Both **2** and **3** can be synthesized from acetylene **4** and aldehyde **5**,[13] shown in Scheme 1.

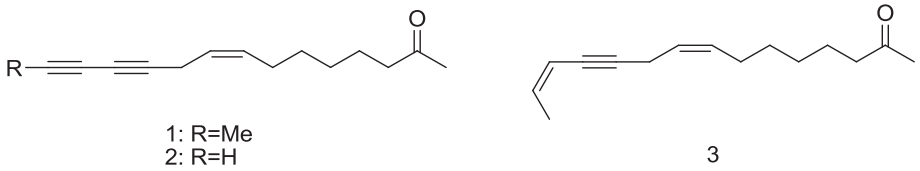

Fig. 1. Structures of 1,2, and 3.

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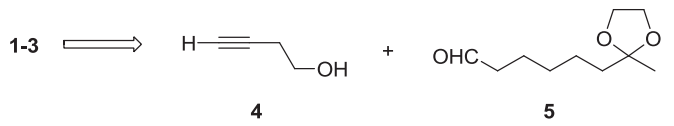
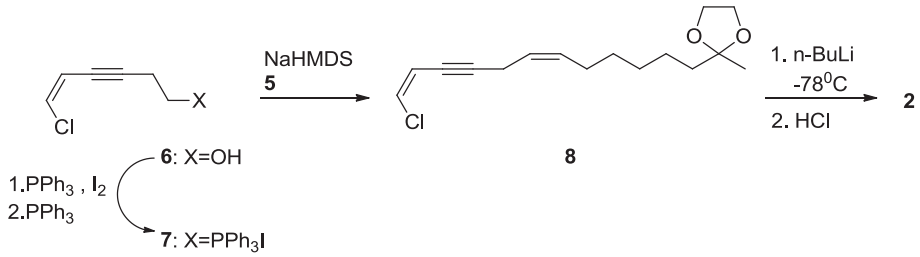


Scheme 1.

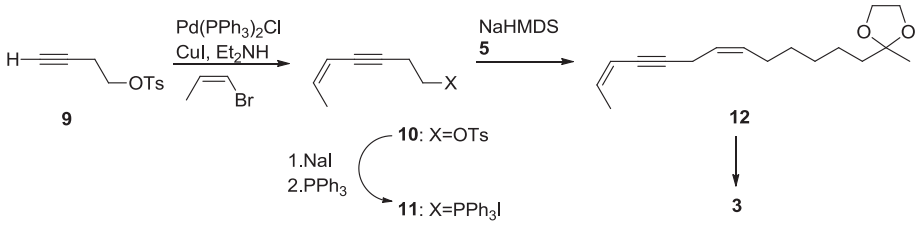
Alcohol **6**, prepared in one step from **4** by the method of Kende,[14] was converted into phosphonium salt **7** in two steps. Phosphonium salt **7** underwent an exclusively cis-selective Wittig reaction[14] with aldehyde **5** to generate a dieneyne **8** in 60% yields. Transformation of the chloroalkene into an acetylene using *n*-butyl lithium at −78 °C[15] was a clean reaction. There was no evidence of products derived from deprotonation of the methylene group between the acetylene and the alkene. The ketal protecting group was removed with HCl, providing ketone **2** in 24% overall yield from **4** over six steps (Scheme 2).



Scheme 2.

Coupling tosylate **9**[16] with cis-1-bromopropene afforded tosylate **10** that could be converted into phosphonium salt **11** in two steps. The cis-selective Wittig reaction of **11** with aldehyde **5** gave ketal **12** in 76% yield. Hydrolysis of ketal **12** with HCl produced ketone **3** in 29% overall yield from **4** over six steps (Scheme 3).

The strategy described above represents a significant improvement over the previous synthetic routes. The route to ketones **2** and **3** is direct and quite flexible with regard to the introduction of additional functional groups.



Scheme 3.

2. Experimental

2.1. (*Z*)-(6-Chlorohex-5-en-3-ynyl)iodotriphenylphosphorane (7)

To 7 mL of dry dichloromethane were added in order: triphenylphosphine (473 mg, 1.8 mmol), imidazole (123 mg, 1.8 mmol), and iodine (458 mg, 1.8 mmol). A solution of compound **6** (217 mg, 1.6 mmol) in 7 mL of dry dichloromethane was added. The mixture was stirred at room temperature under argon for 2.5 h. The solvent was removed in vacuo and the residue was purified by silica gel flash chromatography (hexanes/EtOAc=1:1) to give the iodide (335 mg, 87% yield). A solution of the iodide (335 mg, 1.4 mmol) and triphenylphosphine (367 mg, 1.4 mmol) in 10 mL of acetonitrile was boiled for 24 h. The solvent was removed in vacuo to give compound **7** (711 mg, 100% yield). Compound **7** is pure enough for next step reaction without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 2.83–2.95 (m, 2H), 3.77–3.85 (m, 2H), 5.35–5.38 (d, *J*=9.0 Hz, 1H), 6.09–6.11 (d, *J*=6.0 Hz, 1H), 7.54–7.74 (m, 15H).

2.2. 2-((6*Z*,11*Z*)-12-Chlorododeca-6,11-dien-9-ynyl)-2-methyl-1,3-dioxolane (8)

To a solution of compound **7** (241 mg, 0.50 mmol) in 7 mL of dry THF was added 1.0 M sodium bis(trimethylsilyl)amide (NaHMDS) (0.5 mL) at −78 °C under argon. The mixture was stirred at −78 °C for 20 min. A solution of compound **5** (79 mg, 0.46 mmol) in 3 mL of dry THF was added. The mixture was warmed to room temperature in 1.5 h and stirred at room temperature for 12 h. Saturated NH_4Cl solution was added to quench the reaction. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents in vacuo, the residue was purified by preparative TLC (hexanes/EtOAc=10:1) to give compound **8** (56 mg, 60% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 1.30–1.43 (m, 9H), 1.58–1.65 (m, 2H), 2.03–2.09 (m, 2H), 3.13–3.14 (d, *J*=3.0 Hz, 2H), 3.88–3.98 (m, 4H), 5.41–5.54 (m, 2H), 5.82–5.86 (m, 1H), 6.28–6.31 (d, *J*=9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.3, 24.0, 24.2, 27.4, 29.5, 29.7, 39.4, 64.8, 74.5, 97.5, 110.3, 112.6, 123.6, 127.2, 132.5. HRMS (M+1): calculated for $C_{16}H_{24}ClO_2$: 283.1459; found: 283.1458.

2.3. (*Z*)-Tetradeca-8-en-11,13-diyn-2-one (2)

To a solution of compound **8** (56 mg, 0.2 mmol) in 3 mL of dry THF was added 2.5 M *n*-BuLi (0.08 mL) at −78 °C under argon. The mixture was stirred at −78 °C for 30 min. Saturated NH_4Cl solution was added to quench reaction. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents in vacuo, the residue was purified by silica gel flash chromatography (hexanes/EtOAc=4:1) to give terminal alkyne compound (26 mg, 53% yield). To the solution of terminal alkyne compound (26 mg, 0.11 mmol) in

1.5 mL of THF was added 1.5 mL of 1 N HCl. The mixture was stirred at room temperature for 1 h and quenched with water. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents in vacuo, the residue was purified by flash chromatography (hexanes/EtOAc=4:1) to give compound **2** (19 mg, 89% yield). Both ^1H and ^{13}C NMR spectra of **2** were identical to spectra reported in the literature.[11]

2.4. (*Z*)-Hept-5-en-3-yn-1-yl 4-methylbenzenesulfonate (10)

To a solution of *cis*-1-bromo-1-propene (0.51 mL, 6 mmol) in 12 mL of Et_2NH were added CuI (60 mg, 0.3 mmol) and $Pd(PPh_3)_2Cl_2$ (421 mg, 0.6 mmol) at room temperature under argon. The mixture was stirred at room temperature for 5 min. A solution of compound **9** (1344 mg, 6 mmol) in 18 mL of Et_2NH was added. The mixture was stirred at room temperature for 10 h. The solution was treated with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After removing solvents in vacuo, the residue was purified by flash chromatography (hexanes/EtOAc=4:1) to give compound **10** (872 mg, 55% yield).

^1H NMR (300 MHz, $CDCl_3$): 1.75–1.77 (d, *J*=6.0 Hz, 3H), 2.41 (s, 3H), 2.65–2.71 (td, *J*=3.0, 9.0 Hz, 2H), 4.06–4.11 (t, *J*=9.0 Hz, 2H), 5.31–5.37 (m, 1H), 5.84–5.94 (m, 1H), 7.30–7.33 (d, *J*=9.0 Hz, 2H), 7.75–7.78 (d, *J*=9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.9, 20.5, 21.7, 68.0, 79.4, 88.3, 109.7, 128.0, 130.0, 132.9, 138.5, 145.0. HRMS (M+1): calculated for $C_{14}H_{17}O_3S$: 265.0893; found: 265.0890.

2.5. (*Z*)-Hept-5-en-3-ynyliodotriphenylphosphorane (11)

A solution of compound **10** (116 mg, 0.44 mmol) and NaI (116 mg, 0.77 mmol) in 12 mL of acetone was boiled for 6 h. After cooling to room temperature, the solution was treated with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After removing solvents in vacuo, the residue was purified by flash chromatography (hexanes/EtOAc=4:1) to give the iodide (86 mg, 89% yield). A solution of the iodide (85 mg, 0.39 mmol) and triphenylphosphine (102 mg, 0.39 mmol) in 5 mL of acetonitrile was boiled for 24 h. The solvent was removed in vacuo to give compound **11** (188 mg, 100% yield). Compound **11** is pure enough for next step reaction without further purification.

^1H NMR (300 MHz, $CDCl_3$): 1.46–1.49 (dd, *J*=3.0, 6.0 Hz, 3H), 2.78–2.89 (m, 2H), 3.71–3.79 (m, 2H), 4.82–4.85 (d, *J*=9.0 Hz, 1H), 5.58–5.69 (m, 1H), 7.52–7.70 (m, 15H).

2.6. 2-Methyl-2-((6*Z*,11*Z*)-trideca-6,11-dien-9-ynyl)-1,3-dioxolane (12)

To a solution of compound **11** (188 mg, 0.39 mmol) in 5 mL of dry THF was added 1.0 M sodium bis(trimethylsilyl)amide (NaHMDS) (0.4 mL) at −78 °C under argon. The mixture was stirred at −78 °C for 20 min. A solution of compound **5** (118 mg, 0.63 mmol) in 3 mL of dry THF was added. The mixture was warmed to room temperature in 1.5 h and stirred at room temperature for 12 h. Saturated NH_4Cl solution was added to quench reaction. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents in vacuo, the residue was purified by Preparative TLC (hexanes/EtOAc=4:1) to give compound **12** (78 mg, 76% yield).

^1H NMR (300 MHz, $CDCl_3$): 1.30–1.42 (m, 9H), 1.59–1.64 (m, 2H), 1.82–1.85 (dd, *J*=3.0, 6.0 Hz, 3H), 2.02–2.08 (m, 2H), 3.08–3.09 (d, *J*=3.0 Hz, 2H), 3.87–3.97 (m, 4H), 5.42–5.47 (m, 3H), 5.83–5.93 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 16.0, 18.2, 23.9, 24.2, 27.9, 29.5, 29.7, 39.4, 64.8, 77.1, 93.2, 110.3, 110.5, 124.5, 131.8, 137.4. HRMS (M+1): calculated for $C_{17}H_{27}O_2$: 263.2006; found: 263.2004.

2.7. (8*Z*,13*Z*)-Pentadeca-8,13-dien-11-yn-2-one (3)

To the solution of compound **12** (78 mg, 0.3 mmol) in 4 mL of THF was added 4 mL of 1 N HCl. The mixture was stirred at room temperature for 1 h. Water was added to quench the reaction. The aqueous layer was extracted three times with 5 mL of ethyl acetate. The combined organic layers were dried over Na_2SO_4. After removing solvents in vacuo, the residue was purified by flash chromatography (hexanes/EtOAc=4:1) to give compound **3** (56 mg, 86% yield). Both ^1H and ^{13}C NMR spectra of **3** were identical to spectra reported in the literature.[12]

Acknowledgements

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