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The First Synthesis of a Diynone from *Echinacea pallida*

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Abstract

In order to provide an authentic standard and to generate pure material for biological testing, an efficient synthetic route to **1** was developed. This represents the first total synthesis of a major bioactive diynone from *E. pallida*.

Keywords

diynones; selective alkyne reduction; coupling reaction; selective desilylation

Echinacea extracts are used by millions of people as botanical dietary supplements.¹ While they are purchased primarily to stimulate the immune system, there are many bioactive compounds in the supplements. It is important to have a good understanding of the biological profile of key components of the supplements so that unfavorable drug interactions can be avoided. Most commercial botanical dietary supplements contain mixtures of three of the nine species of *Echinacea*: *E. pallida*, *E. angustifolia* and *E. purpurea*. The chemical fingerprint of *E. angustifolia* has diacetylenic isobutylamides as the diagnostic hydrophobic constituents. In contrast, the chemical fingerprint of *E. purpurea* has tri- and tetraenic isobutyl amides as the most abundant hydrophobic constituents, while *E. pallida* contains acetylenic ketones as the diagnostic hydrophobic constituents. Ketones **1** and **2** represent the most abundant acetylenic ketones of *E. pallida* (Figure 1). Hydroxy ketone **2** is derived from ketone **1** by reaction with molecular oxygen.² Extracts from *E. pallida* also exhibit antiviral activity. Ketones **1** and **2** have been shown to be potent antifungal agents;³ however, the full range of biological activity of these novel compounds has not yet been determined, partly due to the difficulty in obtaining pure **1** from plant extracts containing many other compounds of similar polarity.

As part of an interdisciplinary team of plant scientists, food scientists and chemists whose goal is to identify key bioactive constituents of *Echinacea*,⁴ we describe herein the first total synthesis of ketone **1**. The synthetic route is illustrated below in Scheme 1. Our synthetic route began with the known acetylenic alcohol **3**.⁵ Alcohol **3** was protected as the tetrahydropyranyl (THP) ether **4** in 90% yield (dihydropyran, PPTS, CH₂Cl₂, 0 °C). The protected alcohol was converted into **5** by hydroxymethylation using ethylmagnesium bromide and formaldehyde,⁶ followed by conversion of the alcohol into the iodide using triphenylphosphine and iodine.⁷ The overall yield of **5** from acetylene **4** was 61%. The reaction of iodide **5** with the anion of trimethylsilylacetylene, generated from potassium carbonate and copper iodide, provided diacetylene **6** in 45% isolated yield.⁸ Iodide **5** reacted very slowly with the anion of trimethylsilylacetylene. Yields of 72% for this reaction required potassium carbonate that was dried over phosphorus pentoxide. Surprisingly, the reaction of iodide **5** with the lithium salt of trimethylsilylacetylene, generated via the reaction of the acetylene with *n*-butyllithium, afforded only recovered starting material.

Selective reduction of the internal acetylene in **6** was achieved with P-2 nickel according to the method of Larcheveque in 94% yield.⁹ The trimethylsilyl group undoubtedly played a key role in the regioselectivity. Bromination of the acetylene **7** with NBS in acetone at 25 °C provided the labile bromoacetylene in 72% yield.¹⁰ Coupling of the bromoacetylene with trimethylsilylacetylene using palladium catalysis according to the method of Wityak and Chan afforded diacetylene **8** in 42% isolated yield.¹¹ Deprotection of the THP ether using PTSA in methanol followed by oxidation of the resulting alcohol with PCC and desilylation¹² using silver nitrate and potassium cyanide produced diynone **1** in 60% yield from **8**. Attempted desilylation using tetrabutylammonium fluoride with either the ketone or the protected alcohol **8** led to isomerization of the double bond to a conjugated enyne with a *trans* double bond, as evidenced by the disappearance of the methylene resonance at C-10 which appeared around $\delta = 3.00$ in the NMR spectrum.

The structure of **1** was supported by proton NMR resonances at $\delta = 2.99$ (CH₂ at C-10), 1.97 (H at C-14) and 2.13 (C-1 methyl group). The ¹³C NMR and high resolution mass spectrum also supported the structure.

1-Iodo-9-(2-oxacyclohexyl)oxy-2-decyne (5)

Step 1

To a solution of ethyl magnesium bromide (5.4 mL, 16.3 mmol) in anhyd THF (20 mL) was added a solution of compound **4** (2.44 g, 10.9 mmol) in THF (10 mL) at r.t. The solution was refluxed for 1 h, then cooled to 0 °C and paraformaldehyde (490 mg, 16.3 mmol) was added. The mixture was refluxed for 1 h, then cooled to r.t. and stirred for 12 h. The reaction was quenched with NaHCO₃. The aqueous layer was extracted with CH₂Cl₂, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexanes–EtOAc, 2:1) to provide the propargyl alcohol (2.00 g, 72%).

Step 2

To a solution of imidazole (284 mg, 4.2 mmol) and Ph₃P (1.1 g, 4.2 mmol) in Et₂O–MeCN (12 mL/4 mL) was slowly added iodine (1.1 g, 4.2 mmol) at 0 °C. The resulting slurry was warmed to r.t. and then stirred for 20 min. The slurry was cooled to 0 °C and the propargyl alcohol (964 mg, 3.8 mmol) was added in Et₂O (10 mL) at 0 °C. The solution was slowly warmed to r.t. and then stirred for 1 h. The reaction was quenched by adding hexane (30 mL). The organic layer was washed with aq NaHCO₃, brine, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexanes–EtOAc, 2:1) to give **5** (1.18 g, 85%).

¹H NMR (400 MHz, CDCl₃): δ = 4.69–4.61 (m, 1 H), 3.94–3.70 (m, 2 H), 3.69 (s, 2 H), 3.50–3.46 (m, 1 H), 2.20–2.16 (m, 2 H), 1.83–1.79 (m, 1 H), 1.72–1.65 (m, 1 H), 1.65–1.33 (m, 12 H), 1.20, 1.11 (d, *J* = 6.2 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 98.9, 95.9, 87.0, 86.9, 74.1, 71.3, 63.1, 62.8, 37.6, 36.6, 31.5, 31.4, 29.1, 28.6, 28.5, 25.8, 25.7, 25.6, 25.2, 21.9, 20.4, 20.1, 19.4, 19.3, 19.2, –16.3, –16.4.

HRMS (EI): *m/z* calcd for C₁₅H₂₅IO₂: 364.0899; found: 364.0906.

1-Trimethylsilyl-11-(2-oxacyclohexyl)oxydodeca-1,4-diyne (6)

To a solution of K₂CO₃ (326 mg, 2.36 mmol, freshly dried over P₂O₅) and CuI (205 mg, 1.1 mmol) in DMF (5 mL) was added trimethylsilylacetylene (1.22 mL, 8.6 mmol) and compound **5** (784 mg, 2.15 mmol) in DMF (2 mL) at 0 °C. The solution was warmed to r.t. and stirred

for 24 h. The solution was diluted with Et₂O and aq NH₄Cl (10 mL). The aqueous layer was extracted with CH₂Cl₂, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexanes–EtOAc, 10:1) to give compound **6** (514 mg, 72%).

¹H NMR (300 MHz, CDCl₃): δ = 4.71–4.60 (m, 1 H), 3.92–3.69 (m, 2 H), 3.50–3.46 (m, 1 H), 3.19–3.17 (m, 2 H), 2.19–2.10 (m, 2 H), 1.82–1.30 (m, 14 H), 1.20, 1.07 (d, 3 H, *J* = 6.3 Hz), 0.12 (s, 9 H).

¹³C NMR (75 MHz, CDCl₃): δ = 100.9, 98.8, 95.7, 84.7, 84.6, 81.2, 81.1, 74.1, 73.6, 73.5, 71.2, 62.9, 62.6, 37.6, 36.6, 31.4, 31.3, 29.1, 28.8, 25.8, 25.6, 25.2, 21.9, 20.3, 19.9, 19.3, 18.9, 18.8, 11.0, 0.2, 0.1.

HRMS (EI): *m/z* calcd for C₂₀H₃₄O₂Si: 334.5683; found: 334.5425.

1-Trimethylsilyl-11-(2-oxacyclohexyl)oxydodeca-4-en-1-yne (7)

To a solution of Ni(OAc)₂·4H₂O (47 mg, 0.19 mmol) in EtOH (2 mL) was rapidly added NaBH₄ (8 mg, 0.19 mmol) at r.t. under argon. The flask was filled with H₂ gas and when the gas evolution ceased the active catalyst was poisoned with ethylenediamine (0.025 mL, 0.37 mmol). A solution diyne **6** (313 mg, 0.937 mmol) in EtOH (2 mL) was injected via cannula. The solution was stirred for 2 h and then filtered through Celite. The crude residue was purified via flash column chromatography (hexanes–EtOAc, 10:1) to give compound **7** (289 mg, 94%).

¹H NMR (300 MHz, CDCl₃): δ = 5.46–5.36 (m, 2 H), 4.69–4.59 (m, 1 H), 3.89–3.67 (m, 2 H), 3.49–3.42 (m, 1 H), 2.94 (d, 2 H, *J* = 5.4 Hz), 2.04–1.97 (m, 2 H), 1.81–1.21 (m, 14 H), 1.20, 1.08 (d, 3 H, *J* = 6.3 Hz), 0.11 (s, 9 H).

¹³C NMR (75 MHz, CDCl₃): δ = 132.1, 132.0, 124.1, 124.0, 105.6, 98.8, 95.8, 84.2, 84.1, 74.1, 74.0, 71.3, 63.0, 62.6, 37.7, 36.7, 31.4, 31.3, 29.6, 29.5, 29.4, 27.3, 27.2, 25.9, 25.8, 25.7, 25.5, 22.8, 21.8, 20.3, 19.9, 19.3, 18.6, 0.2.

HRMS (EI): *m/z* calcd for C₂₀H₃₆O₂Si: 336.5814; found: 336.5528.

1-Trimethylsilyl-13-(2-oxacyclohexyl)oxytetradeca-6-en-1,3-diyne (8)

To a solution of compound **7** (265 mg, 0.79 mmol) in acetone (5 mL) was added *N*-bromosuccinimide (210 mg, 1.18 mmol) and AgNO₃ (27 mg, 0.16 mmol) at r.t. After stirring for 1 h at r.t., the mixture was cooled to 0 °C and cold H₂O (5 mL) was added. The aqueous layer was extracted with Et₂O, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (hexanes–EtOAc, 10:1) to give the bromoacetylene compound (204 mg, 72%). To a solution of the bromoacetylene (100 mg, 0.29 mmol), trimethylsilylacetylene (83 μL, 0.58 mmol), (Ph₃)₂PdCl₂ (8 mg, 0.011 mmol), and CuI (2 mg, 0.011 mmol) in THF (6 mL), was added isopropylamine (70 μL, 0.58 mmol) at r.t. under argon. After stirring for 2 h at r.t., the reaction was quenched by adding aq NH₄Cl (3 mL) and the aqueous layer was extracted with Et₂O, washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified via flash column chromatography (hexanes–EtOAc, 10:1) to give compound **8** (44 mg, 42%).

¹H NMR (300 MHz, CDCl₃): δ = 5.57–5.30 (m, 2 H), 4.72–4.58 (m, 1 H), 3.92–3.68 (m, 2 H), 3.00 (d, *J* = 5.4 Hz, 2 H), 2.08–1.99 (m, 2 H), 1.82–1.23 (m, 14 H), 1.21, 1.05 (d, 3 H, *J* = 6.2 Hz), 0.17 (s, 9 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 133.1, 132.5, 123.8, 122.3, 98.8, 95.9, 83.2, 83.1, 78.2, 78.1, 74.1, 74.0, 71.3, 71.2, 68.2, 68.1, 63.1, 62.7, 37.7, 37.6, 36.6, 31.5, 31.2, 29.5, 29.4, 29.3, 27.4, 27.3, 25.9, 25.8, 25.7, 25.5, 21.8, 20.3, 20.0, 19.3, 17.8, 17.1, 0.1.

HRMS (EI): m/z calcd for $\text{C}_{22}\text{H}_{36}\text{O}_2\text{Si}$: 360.6055, found: 360.5938.

Tetradeca-8-en-11,13-diyne-2-one (1)

To a solution of compound **8** (100 mg, 0.28 mmol) in MeOH (5 mL) was added *p*-toluenesulfonic acid (12 mg, 0.014 mmol). The solution was heated at 40 °C for 1 h. It was then cooled to r.t., concentrated, and diluted with H_2O . The aqueous layer was extracted with Et_2O , washed with aq NaHCO_3 , dried (MgSO_4), filtered and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and pyridinium chlorochromate (117 mg, 0.56 mmol) was added at r.t. After 1h, Et_2O (10 mL) was added and the suspension was filtered through Celite. The solvent was concentrated in vacuo and the crude residue was purified via flash column chromatography (hexanes–EtOAc, 2:1) to give TMS-diyne compound (68 mg, 89%). To a solution of the diyne (10 mg, 0.036 mmol) in MeOH (2 mL) was slowly added AgNO_3 (8 mg, 0.047 mmol) in H_2O (1 mL) and MeOH (3 mL) at r.t. After 15 min, KCN (14 mg, 0.216 mmol) in H_2O (2 mL) was added, and the solution was stirred for 10 min. The mixture was extracted with Et_2O , dried (MgSO_4), filtered and concentrated in vacuo. The residue was purified via flash column chromatography (hexanes–EtOAc, 2:1) to give compound **1** (5 mg, 67%) as a light yellow liquid.

^1H NMR (300 MHz, CDCl_3): δ = 5.51–5.37 (m, 2 H), 2.99 (d, J = 6.9 Hz, 2 H), 2.43 (t, J = 7.5 Hz, 2 H), 2.13 (s, 3 H), 2.08–2.01 (m, 2 H), 1.97 (t, J = 1.2 Hz, 1 H), 1.43–1.26 (m, 6 H).

^{13}C NMR (75 MHz, CDCl_3): δ = 209.3, 133.0, 122.2, 77.4, 76.5, 68.6, 65.1, 43.9, 30.1, 29.2, 28.9, 27.2, 23.9, 17.7.

HRMS (EI): m/z calcd: 202.2921 $\text{C}_{14}\text{H}_{18}\text{O}$; found: 202.2806.

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Figure 1.
Ketones isolated from **1** and **2** from *E. pallida*

Scheme 1.