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Phytochemicals from *Echinacea* and *Hypericum*:

A Direct Synthesis of Isoligularone

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Abstract

Reaction of trienes with α,β -unsaturated aldehydes produces bicyclic products via a tandem Diels-Alder/ene reaction. The adduct from tiglic aldehyde was converted into isoligularone by conversion to a furan followed by benzylic oxidation.

Keywords

Diels-Alder; ene reaction; oxidation

Introduction

In the context of developing new tandem radical reactions,^{1–3} we recently discovered a novel tandem reaction involving a Diels-Alder reaction followed by an ene reaction.⁴ Although the initial system studied (**1** and **2**) underwent the tandem reaction either at 80 °C in 56% yield or at 0 °C with catalysis by boron trifluoride etherate in 82% yield, less reactive aldehydes required Lewis acid catalysis.

Because of the endo-selectivity of the Diels-Alder reaction, we anticipated a cis-fused decalin framework in product **3**. NOESY NMR experiments indicated a trans-relationship between the isopropenyl group and the hydroxyl group but did not reveal the relative stereochemistry between the hydroxyl group and the ring juncture. An x-ray structure determination on a related adduct⁵ allowed us to assign retrospectively the relative stereochemistry of **3**. In order to determine the scope of this interesting reaction, an array of dienophiles was treated with trienes. The results of our study showed that excellent stereochemical control could be achieved if X and Y in aldehyde **4** were both methyl groups or if X and Y were connected as part of a ring. Unsaturated ketones reacted with triene **5** to afford Diels-Alder adducts, but the subsequent ene reaction did not occur.

One application of this methodology would be to the synthesis of eremophilane sesquiterpenes.⁶ The sesquiterpene isoligularone (7),⁷ and the eremophilanolides 8⁸ and 9⁹ have been reported. Compound 7 has been synthesized by Yoshikoshi and by Tobinaga using novel Michael addition protocols.¹⁰ Since compounds bearing the 3-acylfuran subunit have shown useful antiviral and anticancer activity, we developed a direct synthesis of this natural product.

Results and Discussion

Our synthetic route begins with adduct **10**. This was prepared in 77% yield as shown below from commercially available aldehyde **11** and triene **12**.

Hydroxyl-directed epoxidation of **10** with *tert*-butylhydroperoxide and molybdenum hexacarbonyl provided a separable mixture of two epoxides which could be reduced (H_2 , Pt/C) and oxidized with the Dess-Martin periodinane to yield **13** and **14** in 65% overall yield from **10** in a ratio of 60:40. Reaction of the major epoxide isomer with sodium hydroxide in ethanol at 25 °C followed by acidification afforded furan **15** in 82% yield. A small amount (5%) of enone **16** was also isolated. The minor epoxide isomer produced **15** and **16** in 20% and 60% yields, respectively. On the basis of the selectivities reported for the molybdenum hexacarbonyl-catalyzed epoxidation of (-)-isopulegol,¹² we tentatively assign the structures of **13** and **14**.

The conversion of furan **15** into isoligularone (**7**) required a benzylic oxidation. Although several methods have been advanced for this transformation,¹³ the application of most of these methods (CrO_3 , $\text{Pb}(\text{OAc})_4$, SeO_2) to **15** led to decomposition of the furan subunit. Fortunately, the use of chromium hexacarbonyl and *tert*-butylhydroperoxide in boiling acetonitrile afforded a 32% yield of **7**.¹⁴ The proton NMR and ^{13}C NMR spectra for **7** matched the literature spectra¹⁵ for isoligularone.

The direct synthesis of **7** nicely demonstrates the utility of the tandem Diels-Alder/ene reaction sequence for the synthesis of natural products. This tandem sequence can create as many as five stereogenic centers in a single reaction. Applications of this chemistry to other natural product ring systems are in progress.

General Procedure for Tandem Diels-Alder/Ene reaction

To a solution of α,β -unsaturated aldehyde (1.1 mmol) in Et_2O (3.5 mL) at 0°C was added $\text{BF}_3\cdot\text{OEt}_2$ (1.1 mmol) and the mixture was stirred for 10 min at 0°C [in case of Et_2AlCl , it was added to aldehyde at -78°C and the mixture was stirred for 10 min at -78°C]. To the resulting yellow solution was added via cannula a solution of triene (1 mmol) in Et_2O (1 mL plus 0.5 mL rinse). After 1 h at 0°C , the reaction mixture was warmed to rt and further stirred for 6 to 19 h (monitored by tlc). The reaction was quenched by the addition of saturated aqueous NH_4Cl (3 mL) and the mixture was extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 , filtered, and was concentrated in vacuo. The residue was purified via silica gel flash chromatography using 5:1 hexanes: ethyl acetate to give the Diels-Alder/ene adduct.

8a-Bromo-2-isopropenyl-6-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (**3**)

^1H NMR (400 MHz, CDCl_3) δ 5.03 (s, 1H), 4.83 (bs, 1H), 4.81 (s, 1H), 3.28 (d, $J = 10.4$ Hz, 1H), 3.01 (bs, 1H), 2.86-2.82 (m, 1H), 2.45 (dt, $J = 10.4, 4.0$ Hz, 1H), 2.28-2.13 (m, 3H), 2.10-1.92 (m, 1H), 1.81-1.73 (m, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.52-1.41 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.4, 135.0, 124.8, 112.8, 81.6, 69.0, 50.7, 45.8, 37.2, 29.8, 28.0, 27.0, 23.0, 19.6; R_f (hexane-EtOAc 5:1) = 0.44; HRMS m/e (EI) for $\text{C}_{14}\text{H}_{21}\text{BrO}$ (M)⁺ calcd 284.0776, measured 284.0780.

2-Isopropenyl-8,8a-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (**10**)

^1H NMR (300 MHz, CDCl_3) δ 5.66-5.61 (m, 1H), 5.34-5.28 (m, 1H), 4.85 (d, $J = 9$ Hz, 2H), 3.57 (d, $J = 10.5$ Hz, 1H), 2.52-2.38 (m, 1H), 2.28-1.95 (m, 2H), 1.80-1.71 (m, 2H), 1.67 (s, 3H), 1.51-1.32 (m, 4H), 0.97 (s, 3H), 0.91 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.6, 130.8, 126.2, 113.1, 70.0, 49.2, 38.7, 32.3, 30.5, 26.9, 26.7, 19.2, 18.1, 15.4; R_f (hexane-EtOAc 5:1) = 0.51; HRMS m/e (EI) for $\text{C}_{15}\text{H}_{24}\text{O}$ (M)⁺ calcd 220.1827, measured 220.1820. Mp 18.7 - 20.2°C .

2-(1-Methyl-2-oxacyclopropyl)-8,8a-dimethyl-decahydronaphthalen-1-one (13/14)

To a solution of alcohol **10** (0.89 g, 4.1 mmol) and $\text{Mo}(\text{CO})_6$ (96 mg, 0.36 mmol) in 10 mL of benzene was added *tert*-butylhydroperoxide (0.84 mL, 5.5M solution in decane) at rt under argon. The reaction mixture was heated to reflux for 1h and then cooled to rt. To the mixture was added 5 mL of 10% $\text{Na}_2\text{S}_2\text{O}_4(\text{aq})$. It was extracted with ethyl acetate (3x20 mL). The organic layer was dried over MgSO_4 , filtered and was concentrated in vacuo. The residue was purified via silica gel flash chromatography using 5:1 hexanes:ethyl acetate to give epoxides (850mg, 80% yield).

To a solution of epoxide (850 mg, 3.6 mmol) in 10 mL of tetrahydrofuran was added Pt-C (1%, 200mg) and the flask was charged with H_2 gas. The mixture was stirred at rt for 1 h and then was filtered through Celite. The filtrate was concentrated in vacuo (809mg, 94% yield).

To a solution of above crude compound (809 mg, 3.4 mmol) in 20 mL of CH_2Cl_2 was added the Dess-Martin periodinane (1.58 g, 3.7 mmol) at 0 °C. The mixture was allowed to warm to rt and stirred for 8 h. To the mixture was added 20 mL of saturated $\text{NaHCO}_3(\text{aq})$ and 20mL of 10% $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$. It was then extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 , filtered and was concentrated in vacuo. The residue was purified via silica gel flash chromatography using 5:1 hexanes:ethyl acetate to give epoxides **13** (418 mg, 52% yield) and **14** (280 mg, 35% yield).

Compound 13

^1H NMR (300 MHz, CDCl_3) δ 2.77 (d, $J = 4.5\text{Hz}$, 1H), 2.55 (d, $J = 4.5\text{Hz}$, 1H), 2.40-2.29 (m, 2H), 2.20-1.91(m, 5H), 1.49-1.33 (m, 5H), 1.30 (s, 3H), 1.25-1.18 (m, 1H), 1.12 (s, 3H), 0.88 (d, $J = 6.8\text{Hz}$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.5, 57.1, 55.9, 53.1, 45.4, 39.4, 31.4, 30.6, 29.7, 26.7, 23.5, 20.5, 17.7, 14.8; R_f (hexane-EtOAc 5:1) = 0.43; HRMS m/e (EI) for $\text{C}_{15}\text{H}_{24}\text{O}_2$ (M) $^+$ calcd 236.1776, measured 236.1771. Anal calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2$: C, 76.23; H, 10.24 Found C, 75.52, H, 10.89.

Compound 14

^1H NMR (300 MHz, CDCl_3) δ 2.71-2.62 (m, 1H), 2.60 (d, $J = 4.5\text{Hz}$, 1H), 2.49 (d, $J = 4.5\text{Hz}$, 1H), 2.41-2.28 (m, 2H), 2.21-1.81(m, 5H), 1.50-1.40 (m, 5H) 1.37 (s, 3H), 1.16 (s, 3H), 0.88 (d, $J = 6.8\text{Hz}$, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 214.5, 56.9, 55.1, 53.5, 51.9, 45.8, 39.4, 32.6, 30.1, 26.0, 25.4, 21.4, 18.1, 14.1; R_f (hexane-Et₂O 5:1) = 0.37. Anal calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2$: C, 76.23; H, 10.24 Found C, 75.98, H, 10.62.

3,9,9a-Trimethyl-4,5,5a,6,7,8,9,9a-octahydro-naphtho[1,2-b]furan (15)

To a solution of compounds **13** and **14** (0.24 g, 1 mmol) in 5 mL of ethanol was added NaOH (4 mg, 0.1 mmol) at rt. The solution was stirred for 8 h at rt. To the solution was added 2 mL of 10% HCl (aq) and it was extracted with ethyl ether (2x10 mL). The organic layer was dried over MgSO_4 , filtered and concentrated in vacuo. The residue was purified via silica gel flash chromatography using 2:1 hexanes:ethyl acetate to give compound **15** (124 mg, 57% yield) and **16** (63 mg, 27% yield).

Compound 15

^1H NMR (400 MHz, CDCl_3) δ 7.04 (d, $J = 1.2\text{Hz}$, 1H), 2.41-2.26 (m, 2H), 2.09-2.04 (m, 1H), 1.91 (d, $J = 1.2\text{Hz}$, 3H), 1.85-1.25 (m, 9H), 1.19 (s, 3H), 0.96 (d, $J = 6.8\text{Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.1, 137.1, 119.5, 116.4, 42.5, 38.9, 36.6, 31.2, 29.9, 27.8, 25.5, 21.5,

20.7, 17.8, 8.4 ; R_f (hexane-EtOAc 2:1) = 0.81 ; HRMS m/e (EI) for $C_{15}H_{22}O$ (M)⁺ calcd 218.1670 , measured 218.1665. The boiling point of **15** was 189-194 °C/40 mm Hg.

Compound 16

¹H NMR (400 MHz, CDCl₃) δ 4.17 (s, 2H), 2.95-2.82 (m, 1H), 2.19-1.95 (m, 4H), 1.85 (s, 3H), 1.70-1.25 (m, 8H), 1.09 (s, 3H), 0.67 (d, J = 6.8Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 203.9, 142.0, 131.1, 62.4, 47.6, 40.2, 33.7, 30.1, 29.2, 28.4, 25.2, 24.0, 18.8, 10.4; R_f (hexane-EtOAc 2:1) = 0.48

Isoligularone (7)

To a solution of compound **15** (73 mg, 0.33 mmol) in 2 mL of acetonitrile was added Cr (CO)₆ (31mg, 0.17mmol) and *tert*-butylhydroperoxide (0.073 mL, 5.5M solution in decane) and then heated to reflux for 7 h. The mixture was cooled to rt and then diluted with ethyl ether (10 mL). It was washed with H₂O, sat NaHCO₃(aq) and brine. The organic layer was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified via preparative TLC using 5:1 hexanes:ethyl acetate to give compound **7** (24 mg, 32% yield).

¹H NMR (400 MHz, CDCl₃) δ 7.07 (d, J = 1.2Hz, 1H), 2.85 (m, 1H), 2.25-2.20 (m, 2H), 2.19 (d, J = 1.2Hz, 3H), 1.61-1.26 (m, 8H), 1.30 (s, 3H), 0.92 (d, J = 6.8Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 196.3, 174.8, 139.3, 119.2, 118.7, 42.3, 41.4, 39.9, 35.0, 30.1, 26.3, 20.6, 17.3, 16.2, 9.4 ; R_f (hexane-EtOAc 5:1) = 0.33 ; HRMS m/e (EI) for $C_{15}H_{20}O_2$ (M)⁺ calcd 232.1463 , measured 232.1466.

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