Industrial Crops & Products 111 (2018) 755–767

Contents lists available at ScienceDirect

Industrial Crops & Products

journal homepage: www.elsevier.com/locate/indcrop

Synthesis and herbicidal activity of 4, 8-DHT and its derivates

Jian-hong Zhang[a,d], Li Yang[a], Xiao Ruan[a], Zhe-liang Sheng[b], Min-fen Yu[c], Bing-song Zheng[e], Jin-yun Zhang[a], Xian-xian Li[a], Ying-xian Zhao[a], Qiang Wang[a,*]

[a] Ningbo Institute of Technology, Zhejiang University, Ningbo, 315100, PR China
[b] Ningbo DAHONGYING University, Ningbo, 315175, PR China
[c] Ningbo Forest Farm, Ningbo, 315440, PR China
[d] Ningbo Academy of Agricultural Sciences, Ningbo, 315040, PR China
[e] College of Forest and Biotechnology, Zhejiang A & F University, Hangzhou, 311300, PR China

ARTICLE INFO

Keywords:
4, 8-DHT
Derivates
Synthesis
Phytotoxic activity
Weeds
Seed germination
Seedling growth

ABSTRACT

The chemosynthesis and potential as green herbicides of 4,8-dihydroxy-1-tetralone (4, 8-DHT) and its derivates were emphatically addressed in this study. Firstly, the synthesis of 4, 8-DHT from commercially available material 1, 5-dihydroxynaphthalene was carried out through a novel route of five reaction steps. Then, its five derivates including 4-benzoyl-8-hydroxy-1-tetralone, 4-(3-hydroxypropoxy)- 8-hydroxy-1- tetralone, 4-(2,3-dihydroxypropoxy)-8-hydroxy-1-tetralone, 4-hydroxy-8-(3-hydroxy propoxy) −1-tetralone and 4-hydroxy-8-(2,3-dihydroxypropoxy)-1- tetralone were prepared by modifying alcoholic and phenolic hydroxyl in C-4 and C-8 position of 4,8-DHT molecular structure. After that, these synthesized compounds were examined for their toxicity against six kinds of weeds (*Lolium perenne*, *Phalaris arundinacea*, *Elymus dahuricus*, *Cichorium intybus*, *Sorghum sudanense*, and *Trifolium repens*) *in vitro*. In general, high concentration could generally inhibit while low concentration might promote the growth of weeds. Among these compounds, 4-(3-hydroxypropoxy)-8 −hydroxy-1-tetralone and 4-hydroxy-8- (3-hydroxypropoxy) −1-tetralone showed significant phytotoxic activities against the six tested weeds, while 4-hydroxy-8-(2,3-dihydroxypropoxy) −1-tetralone was less toxic. For all the six tested weeds, *E. dahuricus* appeared the most sensitive to the treatments of 4, 8-DHT compounds. Hence, it has been suggested that variables including compound type and concentration as well as weed species should be seriously considered in order to develop and utilize the group of 4, 8-DHT compounds as herbicide in future.

1. Introduction

As one of natural chemicals, 4,8-dihydroxy-1-tetralone (4, 8-DHT) was first isolated from a *Scytalidium* species (Findlay and Kwan, 1973), and subsequently this chiral compound in racemic form found in several fungi and plants (Machida et al., 2005; Wu et al., 2011; Li et al., 2014a, 2014b). The two enantiomers of 4, 8-DHT were identified as (−)-(4*R*)-4,8-DHT and (+)-(4*S*)-4,8-DHT, commonly named as regiolone and isosclerone, respectively (Machida et al., 2005; Liu et al., 2007). Recent studies demonstrated some biological properties of 4, 8-DHT, including toxicity to plants (Ciniglia et al., 2012) and cytotoxicity to human cancer cells (Wu et al., 2011; Klaiklay et al., 2012; Salimi et al., 2014; Li et al., 2014a, 2014b). Lately, we also found that 4, 8-DHT isolated from *Carya callicarpa* epicarp could exhibit some dosage-dependent stimulation or inhibition effect on several plant species with of horticultural interests (Li et al., 2014a, 2014b). Besides, an analysis of the phytotoxicity indicated that isosclerone was more toxic to some selected horticultural species than regiolone or racemic 4, 8-DHT (Yang et al., 2016). Based on our previous investigation, the allelochemical 4, 8-DHT seems to have the potential as a natural herbicide (Li et al., 2014a, 2014b; Yang et al., 2016).

Up to now, the solvent extraction method has been widely used to separate 4, 8-DHT from plant species in *Juglans* genus. However, the yield of product provided by traditional method was low, and the process of extraction and purification was complicated (Machida et al., 2005; Li et al., 2014a 2014b). Due to the inevitable trend of artificial synthesis (Beshkar et al., 2017; Razi et al., 2017; Zinatloo-Ajabshir et al., 2017a; Zinatloo-Ajabshir et al., 2017b; Zinatloo-Ajabshir and Salavati-Niasari, 2017), some efforts to synthesize 4, 8-DHT have been made in recent years.

In one study, the 4, 8-DHT was obtained by reduction of juglone (5-hydroxy-1,4-naphthalenedione) with $LiAlH_4$ (lithium aluminium hydride) in THF (tetrahydrofuran), and at the same time, the mixture of sclerone (3,4-dihydro- 4,5-dihy- droxynaphthalen-1(2H)-one) was also

* Corresponding author.
E-mail address: wangqiangsky@263.net (Q. Wang).

https://doi.org/10.1016/j.indcrop.2017.11.051
Received 15 September 2017; Received in revised form 24 November 2017; Accepted 27 November 2017

produced during this process (Fujimoto and Satoh, 1986). Another report described the one-step synthesis of 4, 8-DHT enantiomer (4*S*-isosclerone) starting with juglone and biotransformation by an endophytic fungus, to give the good yield (50%) and high enantio selectivity (98% ee) (Prado et al., 2013). Such the two procedures, however, could be not viewed as the ideal synthetic routes of 4, 8-DHT, because the raw material juglone itself is a natural product which is mainly extracted from plant species in genus *Juglans* and with very low yield (Sharma et al., 2009). The following process of four steps for 4, 8-DHT synthesis was developed by Couche et al. (2003). In which, ethyl 2-(acetoxy)-6-(bromomethyl) benzoate was used as raw material, and 7-(benzyloxy) phthalide was obtained after two steps with good yield (65%). Afterwards, 4, 8-DHT was obtained by hydrolysis of the tandem *Michael-Dieckmann* reaction mixture containing *β*-keto ester with distilled water, while *β*-keto ester was purified by hydrogenolysis over Pd/C in THF to improve the reproducibility. In addition, the reaction efficiency was influenced by the space steric effect due to the formation of a five-membered ring in *Micheal* additive reaction.

In this work, we reported an efficient route for 4, 8-DHT synthesis using commercially available 1,5-dihydroxynaphthalene as raw material. Besides, five derivates were prepared by modification of the phenol or aliphatic hydroxyl groups based on the main structure of 4, 8-DHT, and the herbicidal activities of these new synthesized compounds were evaluated. This study could give an insight to the development of natural, green and more efficient herbicides in future.

2. Experimental

2.1. Materials and chemistry

1,5-dihydroxynaphthalene was purchased from Chembee Company Inc. (Shanghai, China). Seeds of *Lolium perenne*, *Phalaris arundinacea*, *Elymus dahuricus*, *Cichorium intybus*, *Sorghum sudanense*, and *Trifolium repens* were purchased from the market in Ningbo, China, and used for bioassay. Acetonitrile and methanol (spectra analyzed grade) came from TEDIA Chemicals (Charlotte, NC, USA). All other chemicals and solvents in analytical grade were purchased from commercial sources.

^{1}H NMR (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded in NMR spectrometer (Bruker Ac-400 spectrometer), in accordance with the method described previously (Li et al., 2014a, 2014b).

2.2. Synthesis of 4, 8-DHT

Starting with 1,5-dihydroxynaphthalene (1), the synthesis of 4, 8-DHT (6) underwent multi-steps involving several intermediate compounds (2, 3, 4, and 5), as showed in Scheme 1.

2.2.1. Preparation of 1,5-hydroxy-tetralone (2)

At the beginning, 25.2 g NaOH was added into a solution of 1,5-dihydroxynaphthalene (**1**) (100 g) in isopropanol (600 mL). Next, the mixture was transferred into a Parr autoclave (Parr Instrument Company) under 100 psi hydrogen at 80 °C for 20 h. After being cooled to room temperature, the reaction mixture was filtered through a pad of Celite (a diatomite filter, World Minerals Inc.), and then washed three times with 200 mL isopropanol. The combined filtrates were decolorized with charcoal at 50 °C for 1 h, and then were filtered through a pad of Celite. After isopropanol removed, the remaining solution was adjusted to pH = 2 with dropwise addition of HCl, and white solid precipitate appeared. The solid was collected, washed twice with distilled water, and then dried under high vacuum at 50 °C to give a dark brown solid of 1,5-hydroxy-tetralone (**2**), which was used in the next step without further purification.

2.2.2. Preparation of 1, 5-hydroxy-tetralol (3)

The aforementioned 1,5-hydroxy-tetralone (**2**) (5 g) was mixed with $NaBH_4$ (3.5 g) in 50 mL MeOH, and then the mixture was stirred at room temperature for 30 min and quenched by the saturated NH_4Cl solution. The aqueous layer was extracted with AcOEt, the combined organic extract washed with brine, dried with Na_2SO_4 and evaporated, and finally the crude product of 1, 5-hydroxy-tetralol (**3**) was collected for the next step operation.

2.2.3. Preparation of 1,5-dibenzoyl-tetrahydronaphthalene (4)

5.3 g of 1, 5-hydroxy-tetralol (**3**) were dissolved in 63.2 mL of pyridine, and then benzoyl chloride (16.1 mL) was drop by drop added into the solution. The mixture was continuously stirred at room temperature for 20 h, diluted with distilled water, and extracted three times with Et_2O. The organic extract was washed with dilute HCl, $NaHCO_3$ and brine, dried with Na_2SO_4 and evaporated, and finally the produced power of 1,5-dibenzoyl-tetrahydronaphthalene (**4**) was collected for the use in next step.

2.2.4. Preparation of 4,8-dibenzoyl-1-tetralone (5)

10.5 g of 1,5-dibenzoyl-tetrahydronaphthalene (**4**) were dissolved in 47 mL benzene (C_6H_6) at0 °C. Celite (23.6 g), PDC (pyridinium dichromate) (40.2 g) and 70%TBHP (*tert*-butyl hydroperoxide) (67.9 mL) were added into the solution in 15 min. Next, the mixture was stirred at room temperaturefor 24 h, diluted with Et_2O (20 mL), and filtered-through a column of Celite. After the filtration, the Celite column was eluted three times withEt_2O (3 × 10 mL). The filtrate merged from the filtration and the elution was evaporated, and the crude product was purified by column chromatography (silica gel, AcOEt/petroleum ether = 1:5) to give the compound 4,8-dibenzoyl-1-tetralone (**5**) for the next step use.

2.2.5. Production and identification of 4, 8-DHT (6)

5.5 g of 4,8-dibenzoyl-1-tetralone (**5**) were dissolved in EtOH (270 mL), and then Cs_2CO_3 (8.3 g) was added into the solution. The mixture was stirred at room temperature for 2 h, diluted with HCl to adjust pH = 7, and evaporated. The obtained crude product was finally purified by column chromatography (silica gel, AcOEt/petroleum ether = 1:1) to give yellow solid of 4, 8-DHT (**6**) (2.5 g, 98% purity). The synthesized 4,8-DHT was identified by NMR analysis, showing ^{1}H NMR (400 MHz, $(CD_3)_2SO$): 1.98 (m, 1H, 3-C*H*$_2$), 2.20 (m, 1H, 3-C*H*$_2$), 2.75 (m, 2H, 2-C*H*$_2$), 4.75 (m, 1H, 4-C*H*), 5.64 (d, *J* = 4.0 Hz, 1H, 4-O*H*), 6.84 (d, *J* = 8.0 Hz, 1H, 7-C*H*), 7.08 (d, *J* = 4.0 Hz, 1H, 5-C*H*), 7.55 (t, *J* = 8.0 Hz, 1H,6-C*H*), 12.41 (s, 1H, 8-O*H*) (Fig. 1A); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): 31.50 (3-*C*), 35.25 (2-*C*), 66.01 (4-*C*), 115.04 (8′-*C*), 115.87 (7-*C*), 117.45 (5-*C*), 136.80 (6-*C*), 148.66 (4′-*C*), 161.48 (8-*C*), 205.28 (1-*C*) (Fig. 2A).

2.3. Preparation and identification of 4, 8-DHT derivates

A number of analogue compounds were derived by the modification of hydroxyl groups in 4, 8-DHT molecule, as showed in Scheme 2.

2.3.1. 4-Benzoyl-8-hydroxy-1-tetralone (7)

For the operation process (a) in Scheme 2, 843 mg of cesium carbonate (Cs_2CO_3) were added to the solution of 4,8-dibenzoyl-1-tetralone **(5)** (1 g) in MeOH (37 mL), and then the mixture was stirred at room temperature for 2 h, dried under reduced pressure and extracted with AcOEt/water system. The organic extract was washed with brine, dried, and evaporated to give the crude product which was purified by column chromatography (silica gel, AcOEt/petroleum ether = 4:1) to bring out the compound of 4-Benzoyl-8-hydroxy-1-tetralone(0.67 g, 92% purity).

The identification with NMR analysis showed ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 2.36 (m, 1H), 2.46 (m, 1H), 2.88 (m, 1H), 3.00 (m, 1H), 6.32 (m, 1H), 7.00 (m, 2H), 7.54 (t, *J* = 16.0 Hz, 2H) 7.60 (t, *J* = 16.0 Hz, 1H), 7.68 (t, *J* = 16.0 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 12.47 (s, 1H) (Fig. 1B); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.19, 21.07, 31.33, 31.66, 36.71, 60.44, 61.94, 68.03, 69.18, 111.50, 119.39,