

## Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:

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### THE SELECTIVE DEHYDROXYLATION OF 20-HYDROXYECDYSONE BY Zn POWDER AND ANHYDROUS ACETIC ACID

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Version of record first published: 17 Aug 2006.

To cite this article: Wei-Ming Zhu, Hua-Jie Zhu, Wei-Sheng Tian, Xiao-Jiang Hao & Charles U. Pittman Jr. (2002): THE SELECTIVE DEHYDROXYLATION OF 20-HYDROXYECDYSONE BY Zn POWDER AND ANHYDROUS ACETIC ACID, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:9, 1385-1391

To link to this article: <http://dx.doi.org/10.1081/SCC-120003635>

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**THE SELECTIVE DEHYDROXYLATION  
OF 20-HYDROXYECDYSONE BY Zn  
POWDER AND ANHYDROUS  
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Xiao-Jiang Hao,<sup>1,\*</sup> and Charles U. Pittman, Jr.<sup>3,\*</sup>**

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**ABSTRACT**

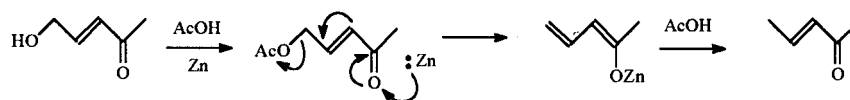
14- $\alpha$ -Deoxyecdysteroids were obtained in an isolated yield of 50% by the one step reduction of 20-hydroxyecdysone with activated Zn powder in anhydrous acetic acid at 65–70°C. About 24% isolated yields of the 14- $\beta$ -deoxyecdysteroid were also obtained.

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20-Hydroxyecdysone, **1a**, is a well-known natural product which exists widely in different plants.<sup>1</sup> It is present in very high content in *Cyanotis arachnoidea* collected in the Yunnan Province of China.<sup>2</sup> Therefore, **1a** is an attractive starting material for the synthesis of 14-deoxy-20-hydroxyecdysones, such as **2a**, if a direct and selective conversion can be developed. 14-Deoxy-20-hydroxyecdysones are very interesting candidates for insect hormone activity based on their structural analogy to 14-dehydroxymuristerone, **6**, which differs from **2a** by the presence of a hydroxy groups at C-11 and C-5. 14-Dehydroxymuristerone, obtained by the treatment of muristerone, **5**, with trimethylsilyl chloride and NaI<sup>3</sup> exhibits an eight-fold greater molting hormonal activity than that of muristerone in assays of the morphological response of cultured Kc-H cells of *drosophila*.<sup>3</sup> Therefore, 14-dehydroxymuristerone has been called a superhormone.<sup>4</sup> The presence or absence of a hydroxyl group at C-14 in this series of analogs and their derivatives is a very important determinant of hormonal activity. 14-Deoxyecdysteroids have been found in the gut and feces of the female adult crickets (*Gryllus bimaculetus*, *Ensifera*, *Gryllidae*) after feeding or injecting the female adult crickets with ecdysone. A mixture of 14-Deoxy-20-hydroxyecdysones, **2a** and **3a**, was also found in the feces after feeding with 20-hydroxyecdysone.<sup>5,6</sup> This strongly suggests that 14-deoxy-20-hydroxy-ecdysones, **2a** and **3a**, could be important biological intermediates. For these reasons, we undertook the modification of 20-hydroxyecdysone to 14-deoxyecdysteroids in order to provide substantial amounts of these 14-deoxy derivatives for biological activity testing.

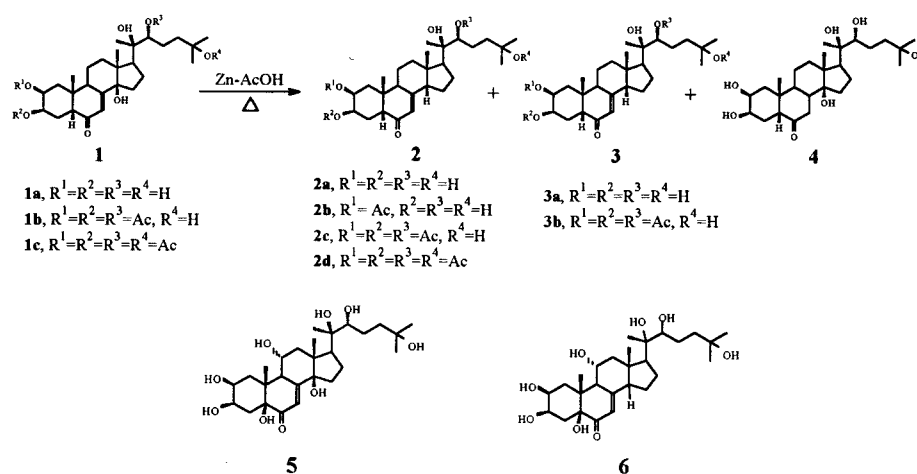
Compound **1a** contains six hydroxyl groups, three of which are tertiary hydroxyls. Therefore, the reduction of only the 14-hydroxy group to its 14-deoxy derivative **2a** presents a selectivity challenge. The 14-hydroxyl group is on the tertiary  $\gamma$ -carbon of an  $\alpha,\beta$ -unsaturated ketone. Conversions of  $\text{HO}-\text{CH}_2-\text{CH}=\text{CR}_2$  to  $\text{CH}_3-\text{CH}=\text{CR}_2$  have been carried out using  $\text{Zn}(\text{Hg}) + \text{HCl}$ ,<sup>7</sup>  $\text{NaBH}_3\text{CH} + \text{ZnI}_2$ <sup>8</sup> or  $\text{LiAlH}_4 + \text{AlCl}_3$ .<sup>9</sup> The general reduction of  $\gamma$ -hydroxyl- $\alpha,\beta$ -unsaturated ketones to  $\alpha,\beta$ -unsaturated ketones with zinc and acetic acid has been investigated and can be represented as shown in Scheme 1.<sup>10</sup>



Scheme 1.

14-Deoxy-20-hydroxyecdysone, **2a**, was previously prepared in only 15% yield when an aqueous solution of 20-hydroxyecdysone, **1a**, was irradiated with 298 nm.<sup>11</sup> Herein, we now report that 14-deoxyecdysteroids can be obtained directly in moderate (~50%) yield by the reduction of **1a** with activated zinc powder in anhydrous acetic acid.

Two methods were used. First, **1a** was treated with 5–10 equivalents of activated zinc powder in anhydrous acetic acid under nitrogen (Scheme 2) at temperatures between 35 and 85°C. After 12 h, the Zn powder was removed by filtration and the volatile contents were evaporated at 10–20 mm Hg at 40°C. The residue was then isolated and the products were purified by column chromatography over silica gel using methylene chloride and ethanol as the elutants. The results are summarized in Table 1.



Scheme 2.

At 65–70°C, reduction of **1a** to **2a** was achieved in 50% isolated yield. This reduction is extremely temperature sensitive, exhibiting a narrow temperature window. Below 40°C, the reduction does not take place (Table 1, Entry 1). At 40°C, most of the substrate was esterified to afford unreduced triacetate, **1b** (90%) and a small amount of reduced **2d** (2%, Entry 2). Above 80°C, the reaction becomes very complex and nonselective (Entry 5). Compound **4**, in which the carbon–carbon double bond had been reduced, was isolated in only 5% yield. In a narrow optimum temperature range (65–70°C), 14-deoxy-20-hydroxyecdysones, **2a** (50%) and **3a** (24%), were obtained in a combined 74% yield (Entry 4). These products differ only in

**Table 1.** Reduction of 20-Hydroxyecdysone, **1a**, with Activated Zn Powder in Anhydrous Acetic Acid

Entry	Temp. (°C)	Time (h)	Yield <sup>a</sup> (%)					<b>2a/3a</b> (14- $\alpha$ : 14- $\beta$ ) <sup>b</sup>
			<b>1b</b>	<b>2a</b>	<b>2b</b>	<b>2d</b>	<b>3a</b>	
1	35	36	—	—	—	—	—	
2	40	12	90	—	—	2	—	
3	60	24	—	15	—	—	8	65:35
4	65–70	12	2	50	2	—	24	67:33
5	85	8	<b>4</b> was isolated with 5% yield					

<sup>a</sup>The yields are based on the isolated products. <sup>b</sup>The ratio of 14- $\alpha$ -deoxy-20-hydroxyecdysone, **2a**, to 14- $\beta$ -deoxy-20-hydroxyecdysone, **3a**, was determined by <sup>1</sup>H NMR integration.

the mode of C/D ring fusion (**2a**, *trans* fusion, **3a**, *cis* fusion). The Zn(OAc)<sub>2</sub> formed in situ catalyzes the esterification of **1a** to give **1c** (2%) and **2b** (2%) in addition to the major products **2a** and **3a**.

In the second method used, **1a** was initially esterified to produce 20-dehydroxy-ecdysone-2,3,22-triacetate, **1b**, by adding Ac<sub>2</sub>O, pyridine and catalytic quantity of DMAP at room temperature. Compound **1b** was then treated with Zn powder in acetic acid at 65–70°C to give **1c** (5% yield), **2c** (8–34%), **2d** (6–8%), and **3b** (5–17%) after isolation and purification by column chromatography. Method 2 is very slow and the yields were lower than for the first method. Thus, if the temperature is not in the 35–85°C range, the reaction does not take place or becomes complex. The best yields of **2c** occurred at 65–70°C.

Product identification employed <sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS (or MS) and IR. In the NOSEY <sup>1</sup>H NMR spectra of **2a**, the resonance at  $\delta$ 0.99 ppm (s, 18-CH<sub>3</sub>) did not give a crosspeak with the resonance at  $\delta$ 2.66 ppm (m, 14-H). However, the resonance of **3a** at 0.97 ppm (s, 18-CH<sub>3</sub>) exhibited a crosspeak with the resonance at 2.88 ppm (m, 14-H), showing that **2a** and **3a** are the 14- $\alpha$ - and 14- $\beta$ -deoxyecdysteroids, respectively.

All nine products, **1b**, **1c**, **2a–d** and **3a–b**, exhibited typical  $\alpha,\beta$ -unsaturated ketone carbonyl absorption at 1650–1670 cm<sup>-1</sup> (IR). Compounds **1b**, **1c**, **2b–d** and **3b** exhibited an acetate carbonyl absorption at 1745 cm<sup>-1</sup>. The absence of absorption in the 1650–1670 cm<sup>-1</sup> range in the IR spectrum of **4** demonstrated the carbon–carbon double bond has disappeared.

Compounds **1b** and **1c** were identified by comparison with their known <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra.<sup>12</sup> The EI-MS fragmentation pattern of **2a**

and **3a** shows that one acetyl group is on the side chain, and two others are on the ring A. The  $m/z$  values obtained from HRMS (M-1) for **2a–d** and **3a–b** match the calculated values. For **2a**, obtained: 463.3045, calculated 463.3059 for  $C_{27}H_{43}O_6$ ; **2b**, obtained, 506.3190, calculated 506.3243 for  $C_{29}H_{46}O_7$ ; **2c**, obtained, 589.3346, calculated 589.3376 for  $C_{33}H_{49}O_9$ ; **2d**, obtained, 632.3516, calculated 632.3560 for  $C_{35}H_{52}O_{10}$ ; **3a**, obtained: 463.3102, calculated 463.3059 for  $C_{27}H_{43}O_6$ ; **3b**, obtained: 589.3434, calculated 589.3376 for  $C_{33}H_{49}O_9$ .

The FAB (M-1)-MS confirms the molecular weight of **4** is 480, indicating two hydrogen atoms were added during the reduction of **1a**. This agrees with the changes from 1650–1670  $cm^{-1}$  to 1690–1730  $cm^{-1}$  in the carbonyl stretching absorptions (IR), as the carbon–carbon double bonds reduction. The HRMS of **4** shows  $m/z$  equals 481.3214 versus a calculated value of 481.3165 for  $C_{27}H_{45}O_7$ . Analogs of **4** have been isolated from plants.<sup>13</sup>

The compounds **2a–d**, **3a–b** and **4** are new compounds and their melting points and specific rotations are listed.<sup>14</sup>

The experimental procedure for esterification of **1a** to **1b**: To the bottle containing **1a** (9.60 g, 20 mmol) was added pyridine (60 ml). After the starting material was dissolved completely,  $Ac_2O$  (20 ml) and a catalytic quantity of DMAP were introduced with stirring at room temperature. After the solution was poured into ice water (200 ml), a precipitate formed and was collected by filtration. The crude solid was recrystallized from a mixture of ethyl acetate and petroleum ether. Pure **1b** (8.88 g) was obtained. The filtrate was column chromatographed (silica gel, mixture of ethyl acetate and petroleum ether) to give additional pure **1b** (0.93 g, total 10.81 g, 89.2% yield) and **1c** (0.222 g, 1.7% yield).

**Method 1:** To a solution of **1a** (960 mg, 2 mmol) and anhydrous acetic acid (12 ml) was added zinc powder (1.28 g, 20 mmol) at 65–70°C. After stirring for 12 h, the residual zinc was filtered and washed with ethanol. The ethanol washings were combined with the acetic acid solution. The solvents then were evaporated at 40°C (10–20 mm Hg) giving a solid which was purified by chromatography over silica gel using  $C_2H_5OH-CH_2Cl_2$  as the elutant. Four purified products were obtained including **2a** (464 mg, 50% yield), **3a** (222 mg, 24% yield), **1b** (120 mg, 2% yield) and **2b** (100 mg, 2% yield).

**Method 2:** To a solution of **1b** (1212 mg, 2 mmol) in anhydrous acetic acid (12 ml) zinc powder (1.28 g, 20 mmol) was added at a temperature of 65–70°C. After stirring for 30 h, the solution was poured into ice water (80 ml). The resulting mixture was extracted three times with  $CH_2Cl_2$ . The combined  $CH_2Cl_2$  layers were washed with saturated aqueous  $NaHCO_3$  and water, respectively, and finally dried over anhydrous  $Na_2SO_4$ .  $CH_2Cl_2$  was removed and the residue was purified by chromatography column over silica gel using a mixture of ethyl acetate and petroleum ether. The pure **2c**

(200 mg, 16.9% yield), **3b** (81 mg, 6.9% yield), **2d** (83 mg, 6.6% yield) and **1c** (60 mg, 4.6% yield) were obtained.

In conclusion, 14- $\alpha$ -deoxy-20-hydroxyecdysone, **2a**, is now readily available in a one step direct synthesis from the abundant natural product 20-hydroxyecdysone, **1a**.

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14. The melting points and specific rotation values for compounds **1b**: m.p. 130–132°C,  $[\alpha]_D^{27} + 46.7$  (*c* 0.300, CHCl<sub>3</sub>); **1c**: m.p. 102–104°C,  $[\alpha]_D^{27} + 56.6$  (90.437, CHCl<sub>3</sub>); **2a**: m.p. 90–92°C  $[\alpha]_D^{27} + 21.6^\circ$  (*c* 0.243, MeOH); **2b**: m.p. 98–100°C,  $[\alpha]_D^{27} + 16.0^\circ$  (*c* 0.313, CHCl<sub>3</sub>); **2c**: m.p. 90–92°C,  $[\alpha]_D^{27} + 26.4^\circ$  (*c* 0.369, CHCl<sub>3</sub>); **2d**: m.p. 81–83°C,  $[\alpha]_D^{27} + 30.7^\circ$  (*c* 0.318, CHCl<sub>3</sub>); **3a**: m.p. 89–90°C,  $[\alpha]_D^{27} + 18.6^\circ$  (*c* 0.218, MeOH); **3b**: m.p. 78–80°C,  $[\alpha]_D^{27} + 13.8^\circ$  (*c* 0.308, CHCl<sub>3</sub>); **4**, m.p. 96–98°C,  $[\alpha]_D^{27} + 24.0^\circ$  (*c* 0.240, MeOH).

Received in the USA May 14, 2001



