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SYNTHESIS AND CHARACTERIZATION OF SEVEN-MEMBERED *β*-KETO ESTERS AS BUILDING BLOCKS TOWARDS ERVATAMINE SYNTHESIS

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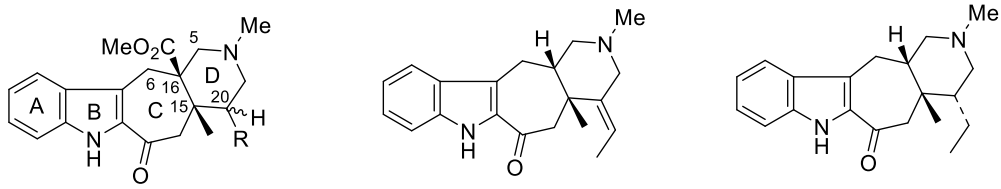
Abstract. In this paper, seven-membered *β*-keto esters were synthesized as initial building blocks for the formation of the C ring and methoxycarbonyl group at C-16 of ervatamine molecule through ring extension process and *α*-hydroxymethylation of 1,4-dioxaspiro[4.5]decan-8-one. Their structures and properties were determined based on ^{1}H NMR, ^{13}C NMR, HSQC, HRMS spectra, and optical rotation measurement.

Keywords: Ervatamine, *β*-ketone ester, 1,4-dioxaspiro[4.5]decan-8-one, ethyl diazoacetate, ring expansion, *α*-hydroxymethylation, building block.

1. Introduction

Ervatamine **1a** and its derivatives **1b** and **1c** were isolated in 1971 by Knox and Slobbe from an Australian tree, Ervatamia orientalis [1], and then synthesized by Husson *et al.* in 1978 [2]. Ervatamine alkaloids such as ervatamine **1a**, 19,20-dehydroervatamine **1c**, methuenine **2**, and silicine **3** form a group of structurally unusual 2-acylindole alkaloids, in which the tryptamine carbons (C5/C6) are in a rearranged state, forming C5-C16 and C6-C16 bonds. The structural feature of these alkaloids is the indole 3-position attached to C-6, a seven-membered C ring included in a *cis*-fused bicyclic system bearing a methoxycarbonyl group at C-16 and an ethyl or (*E*)-ethylidene substituent at C-20 [3, 4].



1a R = Et (20*R*): Ervatamine
1b R = Et (20*S*): 20-Epiervatamine
1c R = Ethylidene: 19,20-dehydroervatamine

2 Methuenine

3 Silicine

Figure 1. Representative alkaloids of the ervatamine-group

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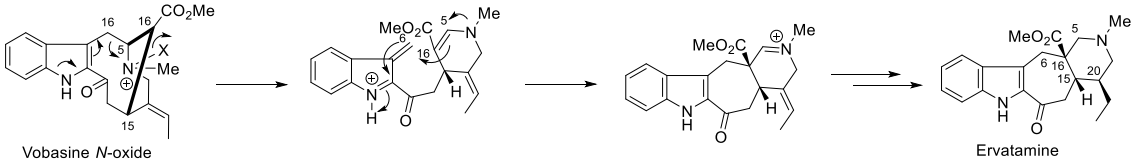
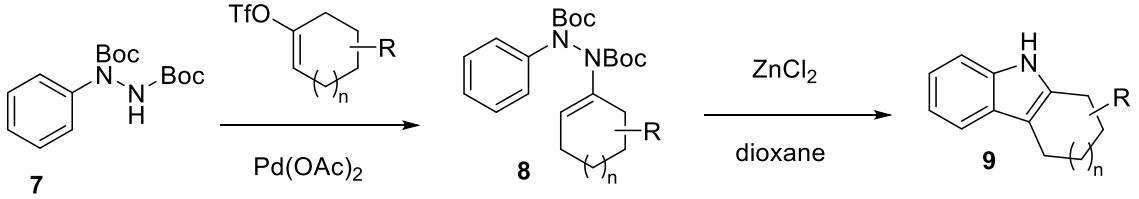
Regarding the biosynthetic pathway, these alkaloids are derived from secologanin via a vobasine *N*-oxide equivalent, undergoing a fragmentation reaction and then a cyclization to form cyclohepta[*b*]indole as the core characteristic of these natural products (Scheme 1) [5].



Scheme 1. Biosynthetic pathway to ervatamine

From a synthetic point of view, studies on ervatamine alkaloids have been directed toward the synthesis of desirable cyclohepta[*b*]indole derivatives [2,4,6,7]. Cho *et al* [8] have developed a novel protocol for the synthesis of highly regioselective polycyclic indole alkaloids based on the Fischer indole reaction, providing the corresponding indole alkaloids via ene-hydrazide which is readily prepared from enol triflate (Scheme 2).



Scheme 2. Ene-hydrazide from Enol Triflate for the Regioselective Fischer Indole Synthesis

In this paper, the structure and characteristics of seven-membered β-keto esters were synthesized and described as building blocks toward ervatamine synthesis.

2. Content

2.1. Experiments

2.1.1. Chemicals

All reagents and solvents were of analytical grade purchased from commercial suppliers and used directly without further purification. Flash column chromatography was performed using silica gel (Kieselgel 60, 230-400 mesh, Merck), and thin-layer chromatography (TLC) was performed using a precoated silica gel 60 F254 (0.25 mm, Merck). Reactions were monitored by TLC (detection with UV light at 254 nm and 365 nm).

2.1.2. Instrumentation

Optical rotation was measured on a Jasco P-2000 polarimeter. High-resolution ESI mass spectra were obtained on a SCIEX X500R QTOF high-resolution mass spectrometer. The $^{1}H/^{13}C$ NMR (600/150 MHz) spectra were recorded in $CDCl_3$ on Bruker AV-600 spectrometer with TMS as an internal standard.

2.1.3. Synthesis

* ***Ethyl 9-oxo-1,4-dioxaspiro[4.6]undecane-8-carboxylate (11) [9]***

To a cooled solution (0 °C) of **10** (1.56 g, 10.0 mmol) and boron trifluoride etherate (2.13 g, 15.0 mmol) in anhydrous diethyl ether (12.5 mL), ethyl diazoacetate (1.88 g, 15.0 mmol) in anhydrous diethyl ether (2.5.0 mL) was added dropwise over 30 min. The resulting solution was stirred under Ar at room temperature overnight, made basic with saturated aqueous sodium carbonate solution, and extracted with chloroform. The chloroform solution was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. Column chromatography of the crude product with acetone: *n*-hexane (2:98, v/v) produced **11** as a light yellow liquid (1.21 g, 50% yield). Keto ester 2 was shown by the following spectral data to exist as a mixture of 70% keto form and 30% enol form:
^{1}H NMR (600 MHz, $CDCl_3$) δ 12.67 (s, 0.45H), 4.25 - 4.13 (m, 3H), 4.00 - 3.92 (m, 6H), 3.52 (dd, J = 9.6, 4.1 Hz, 1H), 2.77 (ddd, J = 14.4, 10.8, 3.4 Hz, 1H), 2.52 (ddd, J = 15.5, 7.9, 3.2 Hz, 1H), 2.49 - 2.45 (m, 1H), 2.44 - 2.40 (m, 1H), 2.20 - 2.12 (m, 1H), 2.11 - 2.04 (m, 1H), 2.02 - 1.86 (m, 3H), 1.80 - 1.71 (m, 3H), 1.68 - 1.62 (m, 1H), 1.31 (t, J = 7.1 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.95, 178.06, 172.64, 170.18, 110.37, 109.46, 108.17, 101.01, 64.55, 64.40, 64.31, 61.21, 60.48, 58.80, 37.07, 37.06, 36.59, 34.16, 33.24, 32.20, 29.41, 22.35, 18.94, 14.26, 14.08. HR-MS (ESI) calcd. For $C_{12}H_{18}NaO_5$ [$(M + Na)^+$]: 265.1052; found: 265.1042.

**** Ethyl 8-(hydroxymethyl)-9-oxo-1,4-dioxaspiro[4.6]undecane-8-carboxylate (12)***

To a solution of **11** (372.9 mg, 1.54 mmol) in THF (3 mL) at 0 °C was added a solution of TEA (43 µL, 0.2 equiv) in THF (0.5 mL) dropwise over 30 min. Then, the reaction mixture was then slowly added to a solution of 37% aqueous formaldehyde (57 µL, 0.5 equiv) in THF (0.5 mL) at the same temperature for 30 min. The mixture was stirred at room temperature for five days. The reaction mixture was added with saturated NH_4Cl (5 mL) and extracted with EtOAc (3 x 20 mL). Combined extracts were dried (Na_2SO_4) and concentrated in a vacuum. Flash chromatography (*n*-hexane/diethyl ether = 88/12) gave alcohol product **12** as a light yellow liquid (330 mg, 68% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.24 (qd, J = 7.1, 1.6 Hz, 2H), 3.99 – 3.91 (m, 5H), 3.75 (d, J = 11.3 Hz, 1H), 3.00 (br s, 1H), 2.79 - 2.73 (m, 1H), 2.65 – 2.58 (m, 1H), 2.22 - 2.16 (m, 1H), 1.99 - 1.88 (m, 3H), 1.84 - 1.78 (m, 1H), 1.77 - 1.72 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.50, 171.69, 109.37, 66.91, 64.62, 64.50, 64.07, 61.69, 37.35, 34.25, 34.06, 25.66, 14.05. HR-MS (ESI) calcd. For $C_{12}H_{20}NaO_6$ [$(M + Na)^+$]: 265.1158; found: 265.1147.

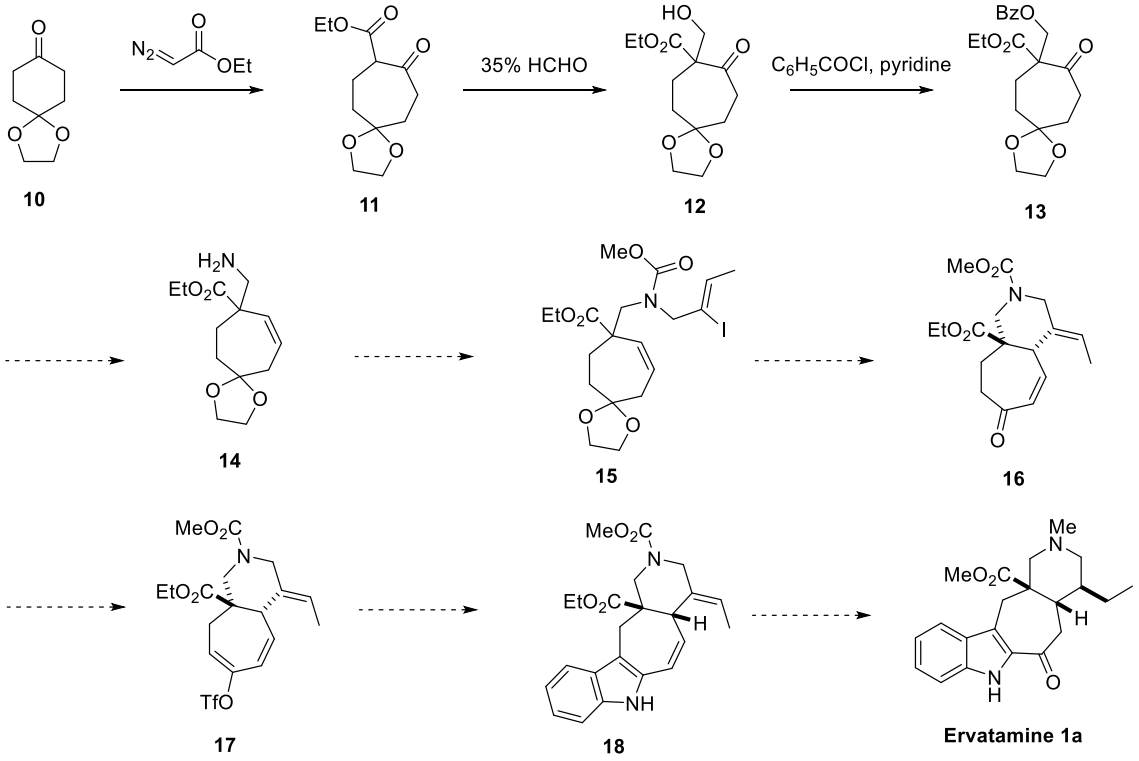
**** Ethyl 8-((benzoyloxy)methyl)-9-oxo-1,4-dioxaspiro[4.6]undecane-8-carboxylate (13)***

To a solution of **12** (148.5 mg, 0.55 mmol) in CH_2Cl_2 (5.5 mL) were added benzoyl chloride (127 µL, 1.1 mmol) and pyridine (222 µL, 2.75 mmol) at room temperature. After stirring for 72 h, the reaction was quenched with saturated $CuSO_4$ solution. The resultant mixture was extracted with CH_2Cl_2 (2x30 mL), and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvents were evaporated, and the residue was purified by preparative TLC (silica gel, Et_2O/*n*-hexane = 2/3) to give the desired product **13** (45 mg, 35% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 - 7.95 (m, 2H), 7.59 - 7.52 (m, 1H), 7.46 - 7.40 (m, 2H), 4.78 (d, J = 11.1 Hz, 1H), 4.56 (d, J = 11.1 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 4.02 - 3.89 (m, 4H), 2.79 (ddd, J = 13.1, 10.1, 2.7 Hz, 1H), 2.61 (ddd, J = 13.3, 9.7, 2.9 Hz, 1H), 2.50 - 2.43 (m, 1H), 2.20 - 2.13 (m, 1H), 2.03 - 1.94 (m, 2H), 1.90 - 1.82 (m, 1H), 1.81 - 1.73 (m, 1H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.18, 169.80, 165.96, 133.15, 129.74, 129.63, 128.44, 109.43, 66.50, 64.65, 64.53, 62.88, 61.93, 37.07, 34.27, 33.76, 25.51, 14.04. HR-MS (ESI) calcd. For $C_{12}H_{24}NaO_7$ [$(M + Na)^+$]: 399.1420; found: 399.1401.

2.2. Results and discussion

Below is our synthetic strategy for the total synthesis of ervatamine (Scheme 3). The known compound 1,4-dioxaspiro[4.5]decan-8-one **11** was selected as our starting material.



Scheme 3. Synthetic strategy of ervatamine

In this paper, we will discuss the synthesis and characterization of seven-membered ring β-ketone ester compounds as an initial building block for the formation of the C-ring and methoxycarbonyl group at C-16 of the ervatamine molecule.

The first step is ring extension of 1,4-dioxaspiro[4.5]decan-8-one **10** with ethyl diazoacetate (16 h) allowing the direct combination of the desired β-keto ester **11** system with high position regioselectivity. The spectral data of compound β-keto ester **11** was compared with the spectral data of the same compound published in the literature [9].

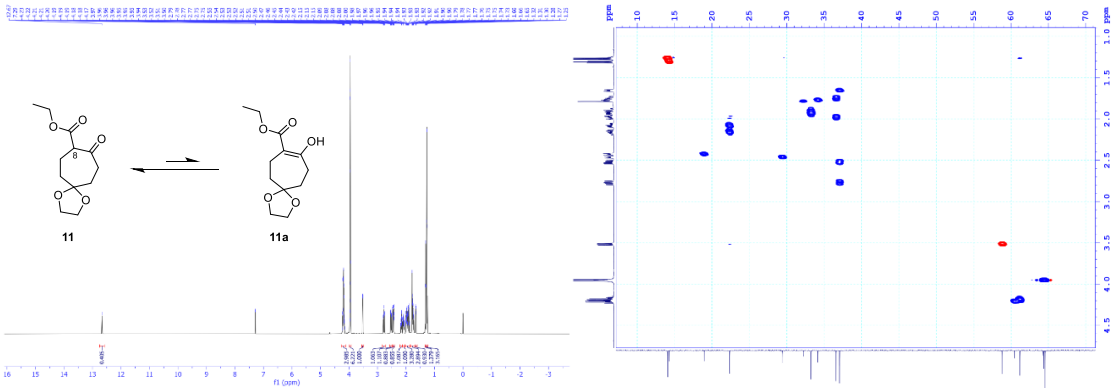
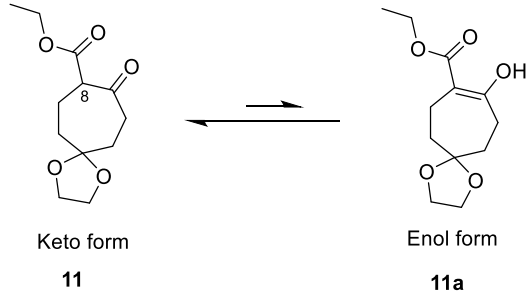


Figure 2. ^{1}H NMR (left) and HSQC (right) spectra of compound 11

On the ^{1}H NMR and HSQC spectra of compound **11** (Fig. 2 and Scheme 4) observed the presence of a signal at 3.52 ppm (dd, J = 9.6, 4.1 Hz) and 1.27 ppm (t, J = 7.2 Hz) assigned to H-8 and -CH_3 proton signals. The singlet signal at 12.67 ppm and the triplet signal at 1.31 ppm with J = 7.1 Hz is assigned to the -OH and -CH_3 proton signals for non-integer numbers of protons, respectively, which indicates that compound **11** exists in a form keto-enol. To determine the keto-enol ratio of **11** in $CDCl_3$ use integral calculus from the simple ^{1}H experiment. In particular, take the integral ratio of the -CH_3 groups of **11** to the integral of the same proton in **11a**, namely the -CH_3 groups at 1.31 and 1.27 ppm. The result for a keto: enol ratio is 2.3:1 (3.165/1.379 = 2.3). This corresponds to a value of 70% in favor of the keto form. Thus, unlike published data in the literature [9], compound **11** exists as a keto-enol tautomerism in $CDCl_3$.



Scheme 4. The keto-enol tautomerism of 11

The next step was the α-hydroxymethylation of β-keto ester **11** with 37% wt formalin aqueous solution catalyzed by TEA (20 mol%). The procedure was carried out at a low temperature (0 ^{o}C to RT) with 0.5 equiv. of 37% HCHO to limit the formation of di-hydroxymethylation, and tri-hydroxymethylation products. α-Hydroxymethylated **12** was obtained with 68% reaction yield.

On the ^{1}H NMR spectrum of compound **12** (Fig 3), there are full resonances of protons present on the molecule. It is easily observed that the wide singlet signal at 3.00 ppm is specific for the hydroxymethyl proton (-CH_2-OH), the signal is specific for the ethyl group (-CH_2-CH_3) at 4.24 ppm (qd, J = 7.1, 1.6 Hz, 2H) and 1.28 ppm (t, J = 7.1 Hz, 3H). The positive HR-ESI-MS spectrum of compound **12** gives the molecular ion peak at 295.1147 $[M+Na]^+$, corresponding to the molecular formula $C_{13}H_{20}O_6$ (calcd. $C_{13}H_{20}NaO_6$ $[(M + Na)^+]$: 295.1158).

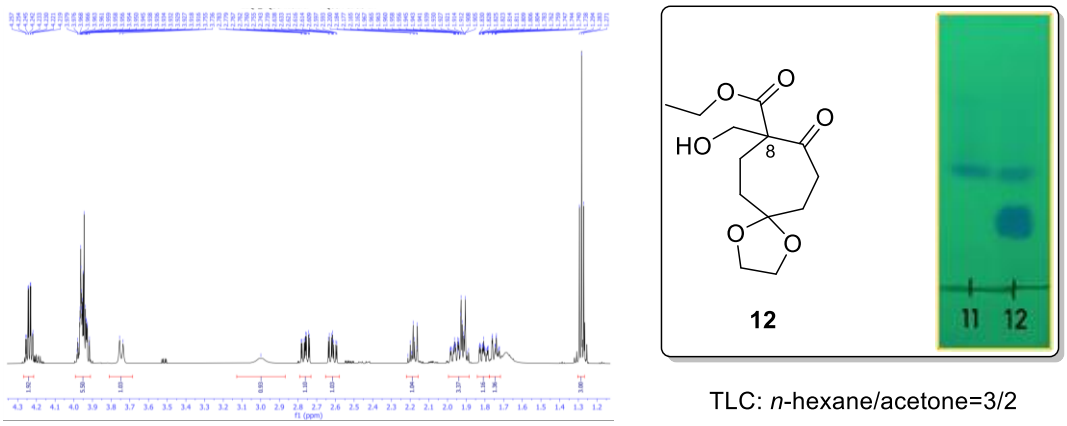
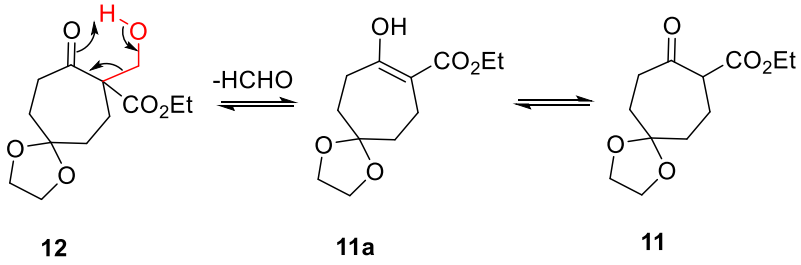


Figure 3. A part of the spectrum of compound 12 in $CDCl_3$ (left) and TLC images of compounds 11 and 12 (n-hexane/acetone=3/2) (right)

The product α-hydroxymethylated **12** is less stable than β-keto ester **11** and converts to a small extent back to its original state. This can be observed in TLC chromatography and traces of the H-8 proton of compound **11** above the ^{1}H NMR spectrum of compound **12** (Fig 3). The decomposition of β-hydroxy ketone with mechanism was believed to proceed through a membered cyclic transition state as shown below [10].



Scheme 5. The unexpected retro-aldol reaction of compound 12

To prevent such an undesired retro-aldol reaction, the hydroxy group in **12** was protected as a base-promoted benzoyl group in DCM yielding product **13** with a 35% yield. The stereoisomer of compound **13** adopts an optical rotation value of zero, confirming the racemic isomerism of compound **12**.

3. Conclusions

In summary, we have synthesized and characterized seven-membered β-keto esters as initial building blocks to form the C ring and methoxycarbonyl group at C-16 of the ervatamine molecule. β-Keto ester (**11**) was synthesized with high regioselectivity via ring expansion of 1,4-dioxaspiro[4.5]decan-8-one (**10**) with ethyl diazoacetate. Spectroscopic data show that β-keto ester (**11**) exists as a mixture of 70% keto form and 30% enol form. The α-hydroxymethylation product (**12**) was obtained through α-hydroxymethylation of β-keto ester (**11**) with 37% formalin aqueous solution, catalyzed by TEA (20 mol%). α-Hydroxymethylation (**12**) shows less stability than β-keto ester (**11**) and partially converts back to the starting material upon flash chromatography column purification. The decomposition of β-hydroxy ketones is thought to be via a retro-aldol reaction. Finally, the hydroxy group of compound (**12**) is protected as a benzoyl

group yielding compound (**13**). The optical rotation experiment of compound (**13**) gave an optical rotation angle value of zero, confirming the racemic isomerism of compound (**12**). The next synthesis steps are being performed in our laboratory.

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