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The first total synthesis of (±)-annosqualine by means of oxidative enamide–phenol coupling: pronounced effect of phenoxide formation on the phenol oxidation mechanism

Hiroki Shigehisa, Jun Takayama and Toshio Honda*

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

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Abstract—The first total synthesis of a spiro-isoquinoline alkaloid, (±)-annosqualine, was established by employing an enamide–phenol coupling of a 1-methylene-1,2,3,4-tetrahydroisoquinoline derivative with a hypervalent iodine reagent, where the formation of the phenoxide was recognized to be an essential step for the reaction of the phenolic hydroxyl group with the hypervalent iodine reagent leading to the formation of the desired product.

Annosqualine **1**, a novel isoquinoline alkaloid with an unprecedented skeleton bearing a spirocyclohexadienone function, was isolated from the stems of *Annona squamosa* in 2004 as a minor component, and was supposed to be a biogenetic precursor of protoberberine and oxoprotoberberine alkaloids.[1] Although the structure of **1** was elucidated spectroscopically, its synthesis and biological activity have not been studied yet (Fig. 1).

Recently, we have developed a facile synthetic procedure for a proaporphine alkaloid, (±)-stepharine, where an oxidative enamide–phenol coupling of an isoquinoline derivative with a hypervalent iodine reagent, iodobenzene diacetate (PIDA) in trifluoroethanol (TFE) leading to the formation of a spirocyclohexadienone moiety, was involved as the key step[2] (Fig. 2).

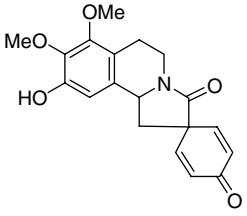

Figure 1. Structure of annosqualine **1**.

In relation to a project directed at the synthesis of biologically active natural products by employing aromatic oxidation with a hypervalent iodine reagent,[3–5] we are interested in establishing a concise synthesis of the unique isoquinoline alkaloid, annosqualine **1**. Prior to the synthesis of the natural product, we decided to investigate efficient and mild reaction conditions for the oxidation of a readily available enamide **5** as follows (Scheme 1).

Condensation of the known 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline hydrochloride **3** with 4-(*tert*-butyldimethylsilyloxy)benzoyl chloride **2**, prepared from 4-(*tert*-butyldimethylsilyloxy)benzoic acid,[6] afforded enamide **4**. Since an attempted isolation of the phenolic enamide **5**, derived from **4** by desilylation with

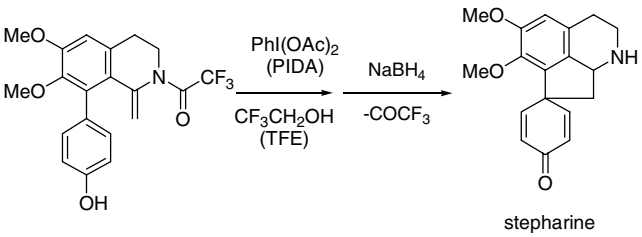

Figure 2. Our previous synthesis of proaporphine alkaloid.

Keywords: Annosqualine; Spiro-isoquinoline alkaloid; Iodobenzene diacetate; Enamide–phenol coupling; Phenoxide formation.
* Corresponding author. Tel.: +81 3 5498 5791; fax: +81 3 3787 0036; e-mail: honda@hoshi.ac.jp

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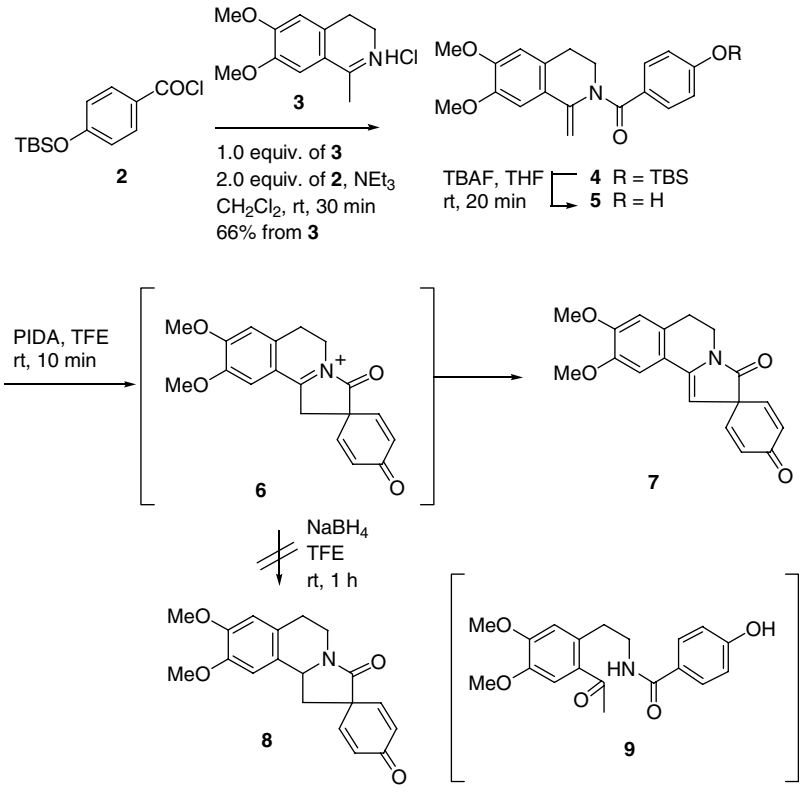


Scheme 1. Preparation of enamide **4** and its conversion to **7**.

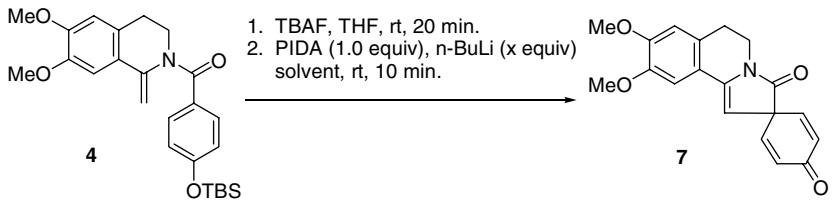
tetrabutylammonium fluoride (TBAF) in tetrahydrofuran, resulted in the easy formation of the hydrolysis product **9**, the crude enamide **5**, obtained from the above reaction mixture by evaporation of the solvent, was subjected to oxidation without further purification.

First, we investigated the oxidation of **5** with the use of PIDA as the oxidant, in TFE at room temperature, and subsequent reduction of the presumed intermediate **6** with sodium borohydride in a one-pot procedure according to our previous procedure;[2] however, none of the desired product **8** could be isolated under these reaction conditions producing only decomposed products. However, we were pleased to be able to isolate enamide **7** by careful examination of the reaction mixture when this oxidation was conducted under the same reaction conditions, without further treatment of an intermediate with sodium borohydride, although the yield was lower than 10%. Encouraged by this result, we next focused our attention on searching for optimal conditions for the oxidation, in which we decided to isolate spiro-enamide **7** instead of its one-pot conversion to **8** by subsequent reduction.

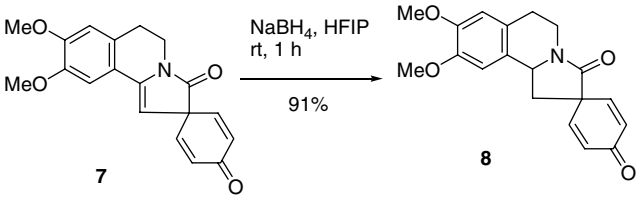
It is well recognized that the use of a solvent with less nucleophilicity gives better result in an oxidative phenolic coupling. Thus, a similar oxidation of **5** with PIDA was carried out in hexafluoroisopropanol (HFIP) as the solvent,[7] instead of TFE; however, the desired spiro-enamide **7** was again obtained in a trace amount. At this point, we had to figure out the reason why the oxidation of **5** did not proceed smoothly to give the desired product, compared to our previous work,[2] where the oxidation gave the desired product in 90% yield. As for this reason, we thought that there are two reactive sites against the oxidant (PIDA), in the starting compound **5**, a phenolic oxygen and an enamide carbon, which might make the oxidation troublesome. Although two reactive sites were also present in the starting material of our proaporphine synthesis, the enamide nitrogen of the starting isoquinoline was protected with a trifluoroacetyl group, a strong electron-withdrawing group, which might diminish the reactivity of the enamide carbon with the oxidant to afford the desired product in high yield. To prove this hypothesis, we decided to add a base to the starting enamide prior to its further oxidation, since generation of the phenoxide by addition of a base would be expected to increase its reactivity against an oxidant. Thus, the starting enamide **5** was treated with 1.0 equiv of *n*-butyllithium in HFIP at 0 °C,[8] and the resulting mixture was reacted with 1.0 equiv of PIDA at room temperature to give the desired spiro-enamide **7** in 38% yield. When this reaction was carried out in the presence of 2.0 equiv of *n*-butyllithium, the yield was improved to 78%. The results obtained are summarized in Table 1.

It is noteworthy that the reaction temperature for the preparation of the phenoxide would be required to be below 4 °C due to the instability of the starting enamide.[9] Moreover, HFIP was obviously better than TFE as the solvent in this reaction. The necessity of 2 equiv of *n*-butyllithium would be attributed to trapping of acetic acid generated from the reagent during the reaction process, in addition to the formation of the phenoxide to increase its reactivity against the oxidant.

Table 1. Oxidation of enamide **4** to the spiro-enamide **7**



Entry	*n*-BuLi (equiv)	Solvent	Yield (%)
1	0	TFE	~10
2	1.0	TFE	12
3	2.0	TFE	~10
4	0	HFIP	~10
5	1.0	HFIP	38
6	1.5	HFIP	60
7	2.0	HFIP	78
8	2.5	HFIP	72
9	3.0	HFIP	69



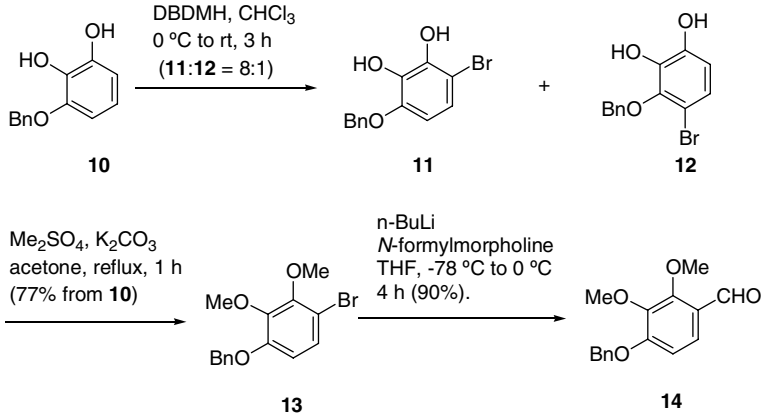
Scheme 2. Reduction of enamide **7**.

With the desired spiro-enamide **7** in hand, we focused our attention on its reduction with sodium borohydride to obtain the basic carbon framework of the natural product. Again, it should be noted that the reduction of **7** with sodium borohydride in methanol, acetic acid, or TFE gave a complex mixture of products, whereas the use of HFIP as the solvent gave the desired product **8**[10] in 91% yield (Scheme 2). Based on consideration of the above results, we attempted a one-pot preparation of **8** from **5** again, as follows.

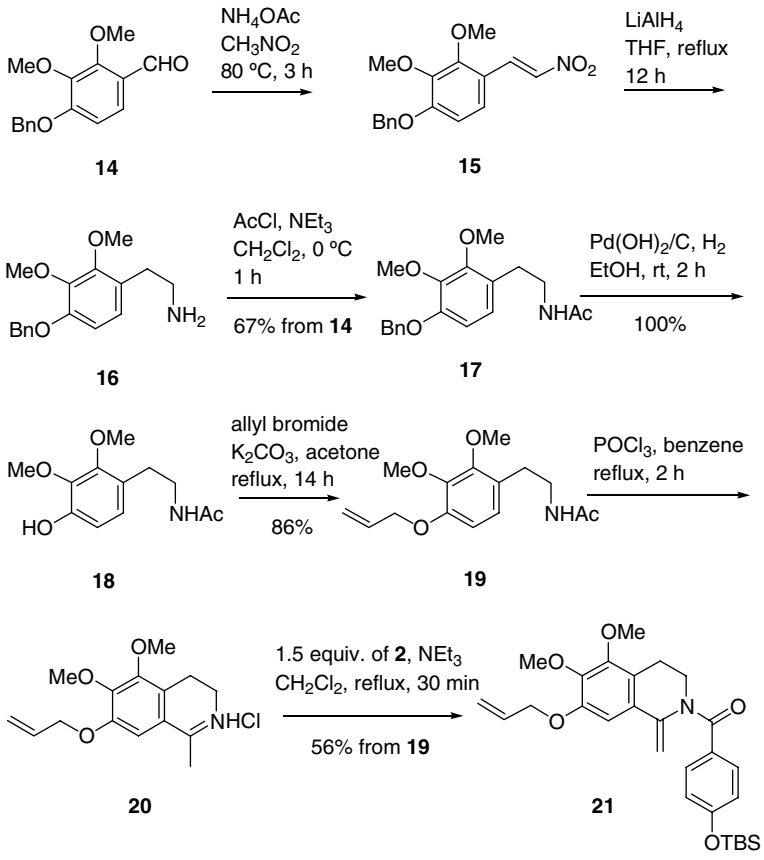
Treatment of **5**, derived from **4** as above, with 2 equiv of *n*-butyllithium in HFIP at below 4 °C, followed by oxidation of the resulting phenoxide with PIDA afforded the intermediate, which, without isolation, was further treated with sodium borohydride to provide the spirocyclohexadienone **8** in 52% yield. Thus, we were able to establish a one-pot synthetic procedure for **8** in reasonable yield.

By establishing a synthetic route to the basic skeleton of the natural product, we started the synthesis of annosqualine as follows. Our synthesis was launched with the preparation of the known aldehyde **14**[11] by an alternative route in improved yield (Scheme 3).

Bromination of monobenzylpyrogallol **10**[12] with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) gave the bromide **11** together with its regioisomer **12**, in a ratio of 8:1.[13] The structure of **11** was unambiguously determined based on its NMR analysis including NOE experiment. After methylation of phenolic oxygen with dimethyl sulfate, the resulting bromide **13** was treated with *n*-butyllithium, subsequently with *N*-formylmorpholine[14] to provide aldehyde **14** in 90% yield. Since we were able to achieve the synthesis of the desired aldehyde **14** in good overall yield, preparation of 1-methyl-3,4-dihydroisoquinoline derivative **20** was then investigated (Scheme 4).



Scheme 3. Preparation of aldehyde **14**.

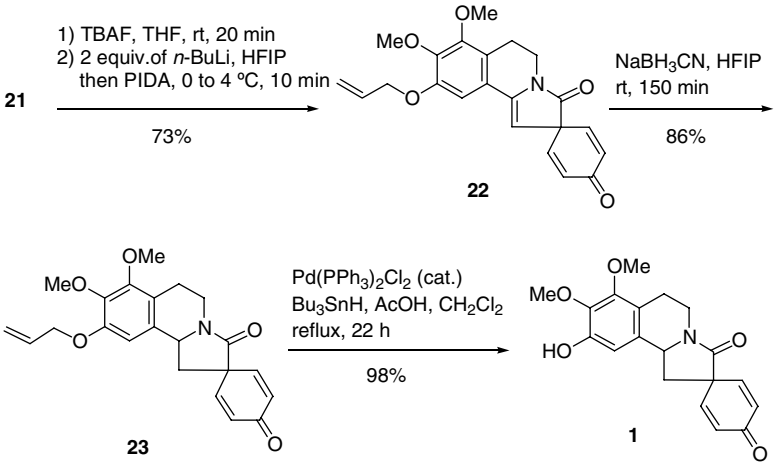


Scheme 4. Preparation of enamide **21**.

Condensation of **14** with nitromethane in the usual manner afforded nitrostyrene **15**, which on reduction with lithium aluminum hydride in refluxing THF furnished phenethylamine **16**. Acetylation of **16** with acetyl chloride gave amide **17** in 67% yield from **14**. Benzyl ether **17** was transformed to its allyl ether **19**, by two steps including a catalytic hydrogenation and allylation of the resulting phenol derivative **18** with allyl bromide in the presence of potassium carbonate, on consideration of the feasibility for its removal at the later stage of the synthesis. Bischler–Napieralski cyclization of **19** with phosphoryl chloride in benzene gave the 3,4-dihydroisoquinoline hydrochloride **20**, which, on treatment with 4-(*tert*-butyldimethylsilyloxy)benzoyl chloride, provided enamide **21** in 56% yield from **19**.

Enamide–phenol coupling of **21**, the key step in this synthesis, was carried out as follows (Scheme 5).

Desilylation of **21** with tetrabutylammonium fluoride in THF afforded the phenolic compound, which, without isolation, was treated with 2 equiv of *n*-butyllithium in



Scheme 5. Synthesis of annosqualine **1**.

hexafluoroisopropanol (HFIP). To this mixture was added iodobenzene diacetate (PIDA) at below 4 °C for 10 min to give spiro-enamide **22** successfully, in 73% yield from **21**. Sodium borohydride reduction of **22** in HFIP gave the reduction product **23**[15] in 60% yield, whereas the use of sodium cyanoborohydride as the reducing agent could improve the formation of **23** to 86% yield.

Finally, deprotection of the allyl group of **23** with a catalytic amount of bis(triphenylphosphine)palladium dichloride and tributyltin hydride[16] afforded (±)-annosqualine **1**,[17] mp 222–223 °C [(+)-natural annosqualine was isolated as a syrup], in 98% yield. The spectroscopic data (^{1}H and ^{13}C NMR) of the synthesized compound were identical with those provided by Professor Wu and Yang.

In summary, we are able to demonstrate the versatility of enamide–phenol coupling by its application to the first total synthesis of a naturally occurring spiro-isoquinoline alkaloid, annosqualine **1**. The strategy developed here would be applicable to the synthesis of various types of alkaloids, and further extension of this strategy is under investigation in this laboratory.

Acknowledgments

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8. Potassium carbonate could also be used for the oxidation; however, the yield (up to 20%) was found to be much lower than that of the case of *n*-butyllithium. The reaction could be carried out in a homogeneous phase by the use of *n*-butyllithium. Similar aromatic oxidation of phenolic compounds with a hypervalent iodine reagent in the presence of sodium hydride was reported, although the reason for the formation of the corresponding phenoxides was not mentioned in the literature. See: (a) de Sousa, J. D. F.; Rodrigues, J. A. R.; Abramovitch, R. A. *J. Am. Chem. Soc.* **1994**, *116*, 9745–9746; (b) Rodrigues, J. A. R.; Abramovitch, R. A.; de Sousa, J. D. F.; Leiva, G. C. *J. Org. Chem.* **2004**, *69*, 2920–2928.
9. Treatment of *n*-BuLi with HFIP probably generated lithium hexafluoroisopropoxide, which on further treatment with **5** gave the corresponding phenoxide. These processes should be carried out at below 4 °C, due to the instability of the phenoxide. When these processes were conducted at room temperature, the starting 3,4-dihydroisoquinoline **3** was recovered as the degradation product.
10. Selected data for **8**: Mp 223–224 °C. FT-IR (film) ν_{max} 1700, 1660, 1520, 1260, 1230, 1100 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (dd, 1H, $J = 12.7$, 9.3 Hz, 9α-H), 2.76 (dd, 1H, $J = 16.1$, 2.6 Hz, 4-H), 2.81 (dd, 1H, $J = 12.7$, 6.5 Hz, 9β-H), 2.97 (ddd, 1H, $J = 16.1$, 11.6, 6.1 Hz, 4-H), 3.16 (br dt, 1H, 3-H), 3.87 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.34 (ddd, 1H, $J = 13.2$, 6.1, 1.9 Hz, 3-H), 5.00 (br t, 1H, 1-H), 6.42 (dd, 1H, $J = 10.0$, 2.9 Hz, 13 or 15-H), 6.45 (dd, 1H, $J = 10.0$, 2.9 Hz, 13 or 15 H), 6.56 (s, 1H, 8-H), 6.67 (s, 1H, 5-H), 6.70 (dd, 1H, $J = 10.0$, 2.9 Hz, 16-H), 6.99 (dd, 1H, $J = 10.0$, 2.9 Hz, 12-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0 (4-C), 38.4 (3-C), 40.0 (9-C), 53.4 (10-C), 53.6 (1-C), 56.0 (OMe), 56.1 (OMe), 107.3 (8-C), 111.8 (5-C), 125.3 (4′-C), 127.5 (8′-C), 130.5 (16 or 17-C), 131.8 (16 or 17-C), 144.4 (12-C), 148.0 (16-C), 148.4 (2C, 6 and 7-C), 168.3 (11-C), 185.3 (14-C); MS [EI+] *m/z* 325 (M^+); HR-MS [EI(+)] calcd for $C_{19}H_{19}NO_4$ (M^+): 325.1314; found 325.1323.
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13. Bromination of 1-benzyloxy-2,3-dimethoxybenzene under the same reaction conditions as described in Scheme 1 gave bromide **11** and its regioisomer **12** in a ratio of ca. 1:1.
14. Formylation of **13** with *n*-BuLi and DMF gave the desired aldehyde in 40–60% yield, and the corresponding primary alcohol was isolated in 30–40% yield, although the mechanism for its formation still remains obscure.
15. Selected data for **23**: Mp 171–172 °C; FT-IR (film) ν_{max} 1700, 1660, 1520, 1100 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.25 (dd, 1H, $J = 12.6$, 9.4 Hz), 2.66–2.72 (m, 1H), 2.77 (dd, 1H, $J = 12.6$, 6.4 Hz), 2.91–2.98 (m, 1H), 3.10 (dt, 1H, $J = 11.7$, 4.6 Hz), 3.89 (s, 3H), 3.90 (s, 3H), 4.30–4.37 (m, 1H), 4.57 (br d, 2H), 4.95 (br dd, 1H), 5.30 (br dd, 1H), 5.42 (br dd, 1H), 5.99–6.13 (m, 1H), 6.39 (m, 3H), 6.70 (dd, 1H, $J = 10.2$, 3.0 Hz), 6.97 (dd, 1H, $J = 10.2$, 3.0 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 22.2, 37.9, 39.7, 53.3, 53.5, 60.7, 60.8, 69.9, 105.0, 117.8, 120.0, 130.4, 131.0, 131.7, 132.9, 141.7, 144.3, 147.9, 151.4, 151.7, 168.1, 185.2; MS [EI+] *m/z* 382 (M^+); HR-MS [EI(+)] calcd for $C_{22}H_{24}NO_5$ (M^+): 382.1654; found 382.1672.
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17. Selected data for the synthetic **1**: Mp 222–223 °C. FT-IR (film) ν_{max} 1700, 1680 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 2.30 (dd, 1H, $J = 12.5$, 9.3 Hz), 2.69 (dddd, 1H, $J = 16.2$, 11.3, 6.2, 1.1 Hz), 2.82 (dd, 1H, $J = 12.8$, 6.8 Hz), 2.90 (ddd, 1H, $J = 16.2$, 4.3, 2.3 Hz), 3.15 (ddd, 1H, $J = 13.2$, 11.3, 4.6 Hz), 3.81 (s, 3H), 3.83 (s, 3H), 4.17 (ddd, 1H, $J = 13.2$, 6.2, 2.3 Hz), 4.61 (s, 1H), 5.06 (dd, 1H, $J = 9.3$, 6.8 Hz), 6.38 (dd, 1H, $J = 10.0$, 3.1 Hz), 6.39 (dd, 1H, $J = 10.0$, 3.1 H), 6.47 (d, 1H, $J = 0.6$ Hz), 6.87 (dd, 1H, $J = 10.0$, 3.1 Hz), 7.22 (dd, $J = 10.0$, 3.1 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 23.2, 39.3, 40.4, 55.0, 55.4, 60.9, 61.0, 108.6, 119.3, 130.5, 132.0, 133.5, 141.3, 147.7, 151.2, 151.3, 152.4, 170.2, 187.7; MS [EI+] *m/z* 341 (M^+); HR-MS [EI(+)] calcd for $C_{19}H_{19}NO_5$ (M^+): 341.1263; found 341.1287.