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SYNTHESIS OF SARMENTOSINE, AN AMIDE ALKALOID FROM *PIPER SARMENTOSUM*

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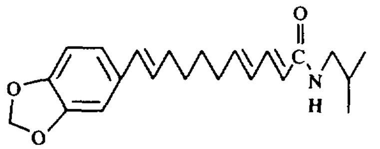
Key Word Index—*Piper sarmentosum*; Piperaceae; sarmentosine; synthesis; aldol; fragmentation; 2-alkenamide; bis[*N*,*N*-bis(trimethylsilyl)amino]-tin (II); selenide; Oxone®.

Abstract—Sarmentosine, 7-(3′,4′-methylenedioxyphenyl)-2*E*,6*E*-heptadienoic acid pyrrolidylamide, isolated from fruit of *Piper sarmentosum*, was synthesized in an overall yield of 21%, by a short efficient pathway in which the key step was an aldol-Grob fragmentation sequence.

INTRODUCTION

Members of the genus *Piper*, (Piperaceae), are endowed with a range of bioactivity that has led to their use in traditional medicine for treatment of a wide variety of conditions [1]. Investigation of constituents of the fruits of *Piper* species has shown that many produce *inter alia*, an array of unsaturated amide alkaloids; indeed the organoleptic properties of *Piper nigrum* that have made it an important spice from antiquity to the present day are due in large part, to the presence of such compounds [2]. Some of these unsaturated amides have generated interest as a result of their potent insecticidal properties [3].

A study in 1987 of components isolated from dried fruit of *Piper sarmentosum* Roxb. [1], led to the isolation and structure determination, of several compounds, including a new member of the class, sarmentosine (**1**) which, to our knowledge has not been synthesized prevously. We recently developed a new efficient synthetic strategy leading to the *Piper nigrum* amides piperide (**2**) and piperolein A (**3**) as well as their *nor*- homologues [4]. The key step in the synthesis of these compounds was a modification of an aldol-Grob fragmentation sequence reported by Sakai in 1993 [5]. This paper reports the synthesis of sermentosine by a short sequence that also employs the above methodology (Scheme 1).



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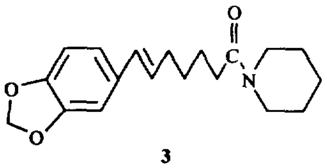

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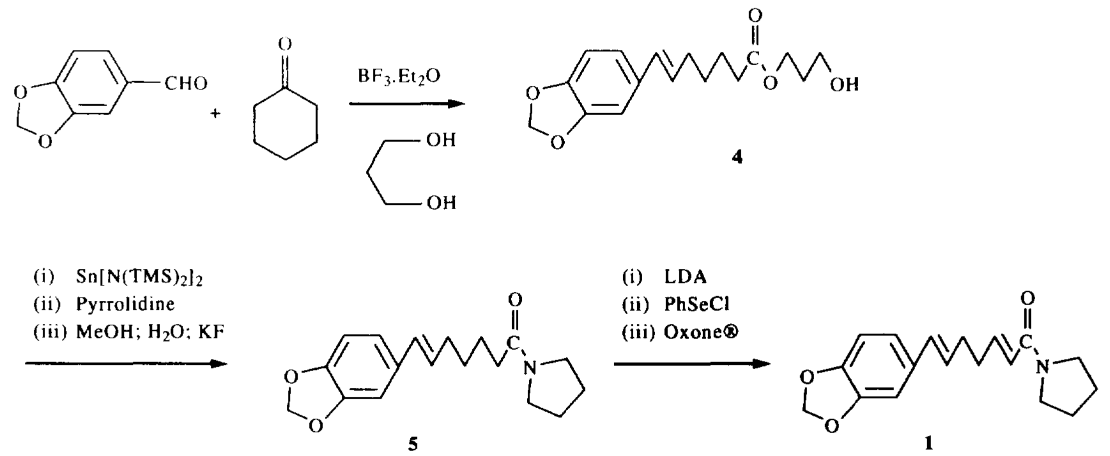
Boron trifluoride-catalyzed reaction of piperonal and cyclohexanone, with subsequent addition of 1,3-propane diol, gave the ester **4** in 43% yield as previously desribed [4]. Grob-type fragmentation of the acetal formed from the initial aldol product has been advanced as the mechanism for such transformations [5]. Analysis of the fragmentation in the context of stereoelectronic considerations dictated the use of 1,3-propane diol rather than ethylene glycol for acetal formation in this system [4]. The propanediol ester **4** is readily convertible to tertiary amides by conventional methodology, involving hydrolysis of the ester and coupling of the resulting acid with the appropriate amine using, for instance, carbonyldiimidazole [4]. Alternatively, conversion of the ester to the amide may be accomplished in high yield in a single step using methodology recently described by Roskamp [6], and the latter process was selected for the present synthesis. Thus, treatment of **4** with bis[*N*,*N*-bis(trimethylsilyl)amino] tin (II)* and pyrrolidine gave, after appropriate work-up, the amide **5** in 87% yield.

The final step required to complete the synthesis of sarmentosine was introduction of the 2,3-double bond. Literature reports of α,β-dehydrogenations of straight chain carboxamides are not abundant, cf. [7]. Back [8] observed that whereas certain 4-azasteroid lactams readily underwent α,β-dehydrogenation through the agency of benzeneseleninic anhydride, attempted desaturation of *N*,*N*-dimethyl-3-phenylpropionamide using this reagent failed. The dehydrogenation procedure of Ghosez [9], involving treatment of amide chlorides with pyridine *N*-oxide and triethylamine appears to require a substituent in the α-position and was unsuccessful, for instance, when applied to *N*,*N*-dimethylbutyramide. In the event, we found that introduction of the 2,3-double bond of **1** could be effected efficiently via α-selenenylation (with phenyl selenenyl chloride) (57%, 79% based on unrecovered starting material), oxidation to the selenoxide and (Ei) elimination [10]. Although oxidation of the



Scheme 1.

α-phenylseleno derivative could be a accomplished in excellent yield with traditional reagents such as hydrogen peroxide or sodium periodate, cf. [10], the reaction was completed most rapidly using Oxone®* (potassium peroxymonosulphate)]. Sarmentosine, **1**, was thus obtained in 56% yield (21% overall from piperonal) and displayed spectroscopic characteristics in full accord with those reported for the natural material [1].

EXPERIMENTAL

Details concerning instrumentation may be found in ref. [4].

7-(3′,4′-Methylenedoxyphenyl)-6E-heptenoic acid pyrrolidylamide, **5**. Glycol ester **4** [4] 175 mg, 0.57 mmol), in dry THF (2.0 ml) and dry hexane (4.0 ml), under an argon atmosphere, was treated with Roskamp reagent, Sn[N(TMS)$_2$]$_2$ [6]*, (0.33 ml, 0.86 mmol) in hexane (6.0 ml). Pyrrolidine (62 mg, 0.86 mmol) in hexane (2.0 ml) was then added, and the mixt. was stirred at ambient temp. until TLC analysis indicated that reaction was complete (3 hr). Work-up was conducted as described [6]. Purification of the crude product, by flash chromatography on silica gel with hexane–EtOAc (1:4) as eluent, furnished amide **5** (159 mg, 87%) as an oil; IR ν_{max} (CHCl$_3$): 2975, 2950, 2875, 1620, 1490, 1440, 1340, 1100, 1040, 960, 940, 910 and 860 cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS, 200 MHz): δ 1.4–1.6 (2H, *m*), 1.6–1.8 (2H, *m*), 1.8–2.0 (4H, *m*), 2.1–2.3 (2H, *m*), 2.26 (2H, *t*, $J = 7.0$ Hz), 3.3–3.5 (4H, *m*) 5.90 (2H, *s*), 6.01 (1H, *dt*, $J = 6.8$ and 15.8 Hz), 6.27 (1H, *d*, $J = 15.8$ Hz), 6.71 (2H, *s*), 6.85 (1H, *s*); HRMS: found: 301.1678; $C_{18}H_{23}NO_3$ requires 301.1678; EIMS [HR] *m/z* (rel. int.): 301 (100) $[M]^+$, 230 (13) $[M - C_4H_9N]^+$, 202 (12) $[M - C_5H_9NO]^+$, 174 (25) $[M - C_7H_{13}NO]^+$, 166 (21) $[M - C_8H_7O_2]^+$, 135 (25) $[C_8H_7O_2]^+$, 131 (24) $[C_9H_7O]^+$, 127 (17) $(C_7H_{13}NO]^+$, 126 (48) $[C_7H_{12}NO]^+$, 113 (97) $[C_6H_{11}NO]^+$, 103 (21) $[C_8H_7]^+$, 98 (17) $[C_5H_8NO]^+$.

7-(3′,4′-Methylenedioxyphenyl)-2-phenylselenyl-6E-heptenoic acid pyrrolidylamide. To a soln of the amide **5** (150 mg), 0.50 mmol) in anhydrous THF (4.0 ml) at −78° under an argon atmosphere was added, dropwise with stirring, a 2.0 M soln of LDA in heptane–THF (0.52 ml, 1.04 mmol). After 35 min, a soln of PhSeCl (105 mg, 0.53 mmol) in dry THF (4.0 ml) was added slowly. The reaction mixt. was set aside with stirring for a further 1 hr at −78°, and was then allowed to attain ambient temp. during 30 min, before being quenched by addition of distilled H$_2$O. The aq. phase was extracted with ether (3 × 50 ml) and the combined extracts were dried over MgSO$_4$ and evapd. to dryness on a rotary vacuum evaporator. The resulting crude yellow oily product was purified by flash chromatography on silica gel with hexane–EtOAc (2:3) as eluent. The pure selenide (130 mg, 57%) was obtained as an oil, and further elution afforded unreacted amide **5** (41 mg). The yield of selenide, based on consumed starting material was 79%.: IR ν_{max} (CHCl$_3$): 2975, 2875, 1620, 1480, 1435, 1040, 960, 935 and 860 cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS, 200 MHz): δ 1.4–1.6 (2H, *m*), 1.7–1.9 (6H, *m*), 2.1–2.3 (2H, *m*), 3.2–3.5 (4H, *m*), 3.80 (1H, *dd*, $J = 6.0$ and 8.6 Hz), 5.93 (2H, *s*), 5.97 (1H, *dt*, $J = 6.8$ and 15.8 Hz), 6.30 (1H, *d*, $J = 15.8$ Hz), 6.72 (1H, *s*), 6.73 (1H, *s*), 6.86 (1H, *s*), 7.2–7.4 (3H, *m*), 7.5–7.6 (2H, *m*); HRMS: found: 457.1143; $C_{24}H_{27}NO_3Se$ requires 457.1157; EIMS [HR] *m/z* (rel. int.): 457 (22) $[M]^+$, 300 (34) $[M - C_6H_5Se]^+$, 201 (17) $[C_{13}H_{13}O_2]^+$, 188 (14) $[C_{12}H_{14}NO]^+$, 174 (8) $[C_{11}H_{10}O_2]^+$, 161 (14) $[C_{10}H_9O_2]^+$, 156 (14) $[C_6H_5Se]^+$, 135 (23) $[C_8H_7O_2]^+$, 131 (28) $[C_9H_7O]$, 126 (100) $[C_7H_{12}NO]^+$, 103 (17) $[C_8H_7]$, 98 (41) $[C_5H_8NO]^+$.

7-(3′,4′-Methylenedioxyphenyl)-2E,6E-*heptadienoicacid pyrrolidylamide, Sarmentosine*, **1**. To a soln of the selenide (130 mg, 0.28 mmol) in THF (5.0 ml) at 0° was added Oxone®* (174 mg, 0.28 mmol) in distilled water (2.0 ml). After the addition was complete, the stirred reaction mixt. was allowed to reach ambient temp. during 15 min. The THF was then removed under red. pres. The residual aq. phase was extracted with Et$_2$O (3 × 50 ml), the com-

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*Commercially available from Aldrich Chemical Company, Inc.

bined organic extracts were washed with satd $NaHCO_3$ soln (20 ml) and dried over $MgSO_4$. Removal of the solvent *in vacuo* then furnished sarmentosine **1**, as an oil (83 mg, 98%), that gradually solidified on standing, mp (uncorrected) 74–79° lit. [1] 77.5–79.5°. The spectroscopic characteristics of the synthetic material were in complete accord with the published data [1].

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REFERENCES

1. Likhitwitayawuid, K. Ruangrungsi, N., Lange, G. L. and Decicco, C. P. (1987) *Tetrahedron* **43**, 3689.
2. Grewe, R., Freist, W., Neumann, H. and Kersten, S. (1970) *Chem. Ber.* **103**, 3752.
3. Miyakado, M., Nakayama, I. and Ohno, N. (1989) in *Insecticides of Plant Origin* (Arnason, J. T., Philogene, B. J. R. and Morand, P., eds), ACS Symposium Series 387, Amer. Chem. Soc. Washington, DC.
4. Strunz, G. M. and Finlay, H. (1994) *Tetrahedron* **50**, 11113.
5. Nagumo, S., Matsukuma, A., Suemune, H. and Sakai, K. (1993) *Tetrahedron* **49**, 10501.
6. Wang, W.-B. and Roskamp, E. J. (1992) *J. Org. Chem.* **57**, 6101; Wang, W.-B., Restituyo, J. A. and Roskamp, E. J. (1993) *Terahedron Letters* **34**, 7217.
7. Larock, R. C. (1989) *Comprehensive Organic Transformations*. VCH New York.
8. Back, T. G. (1981) *J. Org. Chem.* **46**, 1442.
9. Da Costa, R., Gillard, M., Falmagne, J. B. and Ghosez, L.(1979) *J. Am. Chem. Soc.* **101**, 4381.
10. Clive, D. J. (1978) *Tetrahedron* **34**, 1049.