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LETTERS TO THE EDITOR

Stereoselective Synthesis of Sarmentine

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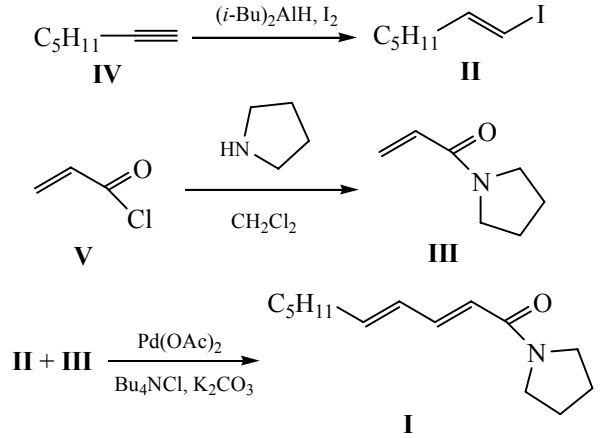
Natural (2*E*,4*E*)-dienamides of *Piperaceae* and *Echinacea* species have a broad spectrum of therapeutic action, and in the past decade they attracted a wide attention [1–7]. Sarmentine, the 1-[(2*E*,4*E*)-deca-2,4-dienoyl]pyrrolidine, was first isolated from the *Piper sarmentosum* fruits [8]. It possesses sedative, analgesic, and antibacterial activities [9]. Recently it was found to manifest antitubercular and antiplazmodial activities [10].

The main task in a sarmentine synthesis is the stereoselective construction of conjugated (2*E*,4*E*)-diene system bonded with the amide function. Previously for this purpose were used the elimination [11] and homologenization of (2*E*,4*E*)-pentadienyl-1-carbonyl precursors [12, 13], isomerization of alkynylamides [14] and stereoselective iodosulfonylation of (2*E*,4*E*)-pentadienamide followed by the cross-coupling with *n*-pentylmagnesium bromide [15]. These methods are characterized by the low overall yield of the target product and the low stereoselectivity.

We investigated the possibility of stereoselective synthesis of 1-[(2*E*,4*E*)-deca-2,4-dienoyl]pyrrolidine **I** on the basis of direct cross-coupling of (1*E*)-1-iodohept-1-ene **II** with 1-acryloylpyrrolidine **III** (the Mizoroki–Heck reaction) [16–19]. The initial (1*E*)-1-iodohept-1-ene **II** was obtained via the hydroalumination-iodination of 1-heptyne **IV** in an yield of 88% by the optimized procedure [20]. The other building-block in the cross-coupling reaction, 1-acryloylpyrrolidine **III**, was synthesized through the acrylic acid chlorodehydroxylation followed by the amidation of acryloyl chloride **V** with pyrrolidine.

The reaction of (1*E*)-1-iodohept-1-ene with 1-acrciloylpyrrolidine in the presence of $Pd(OAc)_2$, a base, and tetrabutylammonium chloride in DMF yields quantitatively 1-[(2*E*,4*E*)-deca-2,4-dienoyl]pyrrolidine with an insignificant content of isomeric products (1%). The total yield of the desired product is 83% relative to the starting 1-heptyne.



The structure and stereochemical purity of sarmentine **I** was confirmed by the ^1H and ^{13}C NMR spectrometry, GLC analysis, and gas chromatography–mass spectrometry. In the ^1H NMR spectrum of the product **I** the coupling constants of vinyl hydrogen atom at C^2 atom is 7.14 Hz, which indicates clearly the double bond of transoid configuration.

The IR spectra were recorded from a thin layer on a Prestige-21 Shimadzu IR-Fourier spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument operating at 300 and 75.47 MHz, respectively) from solutions in $CDCl_3$. The chromatographic and mass spectral analysis was performed on a Chromatec-Crystal 5000 complex equipped with a Finnigan DSQ mass-selective detector (electron impact at 70 eV). A Restek Rtx-5ms capillary column (5% diphenylpolysiloxane, 95% dimethylpolysiloxane, length 30 m) was used, the evaporator temperature 250°C, the ionization cell temperature 250°C. The analysis was carried out with programming temperature from 50 to

250°C at a heating rate 10 deg min^{-1}, carrier gas helium (1.1 ml min^{-1}).

(1*E*)-1-Iodohept-1-ene (II) was obtained by the modified procedure [20]. To a solution of 0.96 g of 1-heptyne **IV** in 10 ml of anhydrous hexane 15 ml of 1 M diisobutyl aluminum hydride solution in hexane was added. The mixture was stirred for 6 h at 55°C in an argon atmosphere and cooled to –50°C. Then to this mixture a solution of 2.79 g of iodine in 10 ml of anhydrous THF was added over 30 minutes. The reaction mixture was warmed within 1 h to room temperature and stirred at this temperature for another 12 h. To the mixture 25 ml of 10% sulfuric acid solution was added under ice-cooling. The organic layer was separated, and the aqueous layer was extracted with hexane (3×15 ml). The combined organic solutions were washed with brine, dried over Na_2SO_4, and concentrated. The product was isolated by the column chromatography (SiO_2, hexane–chloroform, 6:1). Yield 1.98 g (88%). IR spectrum, ν, cm^{-1}: 2955, 2924, 2855, 1605, 1458, 1209, 1173, 939. ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3), 1.21–1.43 m (6H, $3CH_2$), 2.03 q (2H, $C\underline{H}_2CH$=, *J* 6.9 Hz), 5.96 d (1H, C^1H=, *J* 14.4 Hz), 6.45–6.54 m (1H, C^2H=). ^{13}C NMR spectrum, δ_C, ppm: 13.91 (C^7), 22.33 (C^6), 27.96 (C^4), 31.02 (C^5), 35.93 (C^3), 74.24 (C^1), 146.65 (C^2). Mass spectrum, *m*/*z* (I_{rel}, %): 224 (34) $[M]^+$, 167 (24), 154 (55), 97 (22), 69 (13), 55 (100), 41 (23), 39 (13).

1-Acryloylpyrrolidine (III). To a solution of 1.81 g of acryloyl chloride **V** in 20 ml of anhydrous dichloroethane was slowly added 2.84 g of pyrrolidine in 15 ml of anhydrous dichloroethane at 0–5°C. The reaction mixture was stirred for 3 h at room temperature. The precipitate was filtered off and washed with dichloromethane (2×10 ml). The organic layer was successively washed with 10 ml of water, 2 ml of 5% HCl solution, 2 ml of $NaHCO_3$ saturated solution, and dried over Na_2SO_4. The solvent was removed, and the crude product was purified by the column chromatography (SiO_2, hexane–ethyl acetate, 5:1→1:1). Yield 1.38 g (55%). IR spectrum, ν, cm^{-1}: 2972, 2872, 1647, 1609, 1436, 1375, 982, 797. ^{1}H NMR spectrum, δ, ppm: 1.65–1.85 m (4H, $2CH_2$), 3.31–3.40 m (4H, 2 CH_2N), 5.48 d (1H, CH_2=, *J* 10.1 Hz), 6.12–6.35 m (2H, CH_2=, CH=). ^{13}C NMR spectrum, δ_C, ppm: 23.67 (CH_2), 25.53 (CH_2), 45.24 (CH_2N), 45.96 (CH_2N), 126.46 (CH_2=), 128.38 (CH=), 163.76 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 125 (75) $[M]^+$, 124 (36), 97 (14), 96 (24), 70 (39), 69 (32), 68 (18), 56 (13), 55 (100), 43 (12), 42 (19), 41 (22), 39 (14).

1-[(2*E*,4*E*)-Deca-2,4-dienoyl]pyrrolidine (I). To a mixture of 0.46 g of K_2CO_3, 0.37 g of Bu_4NCl, 0.3 g of (1*E*)-1-iodohept-1-ene **II**, and 0.25 g of 1-acryloylpyrrolidine **III** in 0.9 ml of DMF was added a solution of 0.006 g of $Pd(OAc)_2$ in 0.1 ml of DMF. The reaction mixture was purged with argon and heated for 5 h at 70°C under stirring. After consumption of (1*E*)-1-iodohept-1-ene **II** (TLC control), 3 ml of water and 3 ml of hexane was added to the mixture. The organic layer was separated, and the aqueous layer was extracted with hexane (2×3 ml). The combined organic solutions were washed with water (5 ml), dried over Na_2SO_4, and concentrated. The crude product was purified by the column chromatography (SiO_2, hexane–ethyl acetate, 9:1→4:6). Yield 0.28 g (94%). IR spectrum, ν, cm^{-1}: 2955, 2926, 2870, 1653, 1624, 1600, 1425, 999. ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3), 1.26–1.47 m (6H, 3 CH_2), 1.81–2.03 m (4H, 2 $\underline{CH}_2CH_2N$), 2.15 q (2H, $C\underline{H}_2CH$=, *J* 7.0 Hz), 3.46–3.58 m (4H, 2 CH_2N), 6.02–6.23 m (2H, 2 CH=), 6.10 d (1H, C^2H=, *J* 14.7 Hz), 7.22–7.35 m (1H, CH=). ^{13}C NMR spectrum, δ_C, ppm: 13.76 (C^{10}), 22.24 (C^9), 24.10 ($\underline{C}H_2CH_2N$), 25.86 ($\underline{C}H_2CH_2N$), 28.23 (C^7), 31.11 (C^8), 32.69 (C^6), 45.57 (CH_2N), 46.17 (CH_2N), 119.66 (C^2), 128.50 (C^4), 141.86 (C^5 or C^3), 142.79 (C^3 or C^5), 164.89 (C^1). Mass spectrum, *m*/*z* (I_{rel}, %): 221 (22) $[M]^+$, 151 (29), 150 (100), 98 (27), 95 (26), 81 (76), 70 (46), 69 (30), 67 (27), 55 (36), 53 (23), 41 (28).

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