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A New Straightforward and General Approach to Dienamide Natural Products

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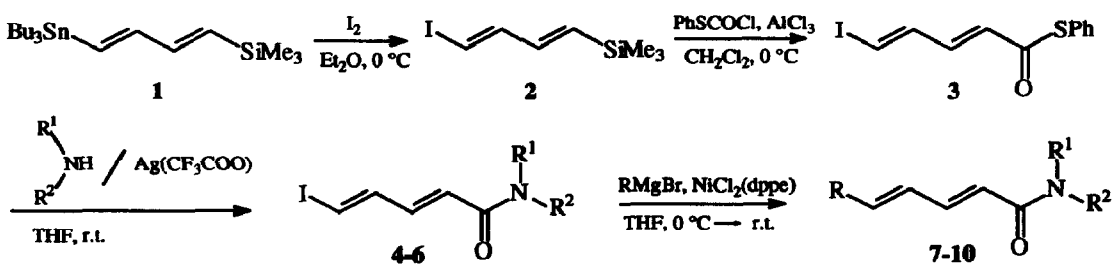
Abstract: A new synthetic approach to various conjugated (*E,E*) dienamides has been developed, starting from an easily accessible bifunctional dienyl compound and based upon a double selective electrophilic substitution, followed by coupling reactions.

Dienamides with a conjugated (*E,E*) structure represent important structural features of a number of natural products, which show both physiological and insecticidal activities.[1] The methods used for their synthesis involve the Wittig type approach,[2] elimination reactions of β-substituted sulfones[3] and allylic acetates,[4] the isomerization of the corresponding 2-ynoic amides under the catalysis of ruthenium or iridium complexes[5] and the addition of organometallic reagents to silylated aldehydes.[6]

In continuation of our studies on the synthesis of stereodefined olefinic systems,[7] we have recently devised a new synthetic approach, based upon the chemoselective and sequential substitution of the trimethylsilyl groups of conjugated dienyl and trienyl disilyl derivatives with acyl chlorides,[8] which has been successfully applied to the synthesis of a series of natural products with a conjugated polyenyl structure.[9] Now, we wish to report a new and straightforward stereoselective procedure for the synthesis of dienamide natural products.

The methodology is based upon the preparation and the reactions of the new building block **1**, (1*E*,3*E*)-4-tri-*n*-butylstannyl-1-trimethylsilyl-1,3-butadiene. Indeed, we have found that this compound can be conveniently obtained[10] and the two groups present on the terminal positions can be chemo- and stereo-selectively substituted with electrophilic reagents. Thus, (scheme 1), the reaction with iodine occurs with high retention of configuration and leads to the iodo-silyl derivative **2**.

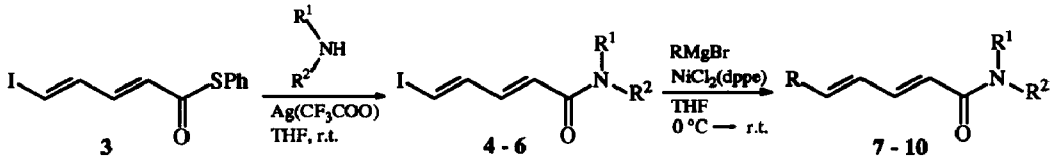
Scheme 1



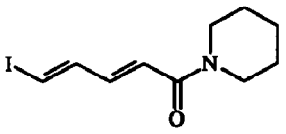
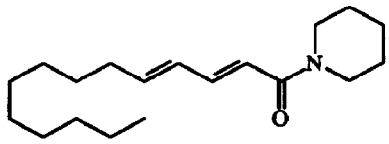
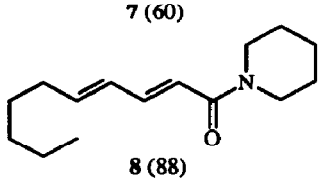
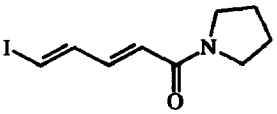
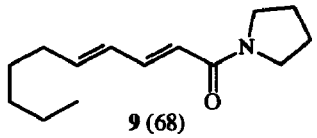
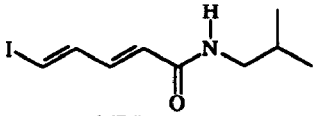
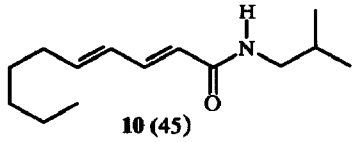
The subsequent electrophilic substitution of the silyl group with phenyl chlorothioformate affords the thioester **3** which represents the key intermediate for the synthesis of various dienamides. As reported in the

Table, a simple conversion of the same thioester **3** in different amides **4-6**, followed by cross-coupling reactions with various Grignard reagents in the presence of transition metals, leads to the desired dienamides **7-10** (stereoisomeric purities in the range 95-97%, capillary GC analysis).[11]

Table. Synthesis of (2*E*,4*E*)-dienamides **7-10**



3 **4 - 6** **7 - 10**

R^1	R^2	Iododerivatives **4-6** (yield %)[a]	R	Dienamides **7-10** (yield %)[a]
-$(CH_2)_5$-		 **4** (57)	C_9H_{19}	 **7** (60)
-$(CH_2)_5$-		**4**	C_5H_{11}	 **8** (88)
-$(CH_2)_4$-		 **5** (63)	C_5H_{11}	 **9** (68)
H	$(CH_3)_2CHCH_2$	 **6** (76)	C_5H_{11}	 **10** (45)

a) yields refer to products purified by flash chromatography (silica gel, petroleum ether:EtOAc 8:2); satisfactory ^{1}H-NMR and mass spectra were obtained for all new compounds.

In particular, the procedure was applied to the synthesis of N-(2*E*,4*E*-tetradecadienoyl)-piperidine **7**,[5] isolated from *Othantus maritimus*,[1b] N-(2*E*,4*E*-decadienoyl)-piperidine **8**,[5] *Achillea* amide,[1a] N-(2*E*,4*E*-decadienoyl)-pyrrolidine **9**,[6] sarmentine, recently isolated from *Piper sarmentosum*,[1g] and (2*E*,4*E*)-N-isobutyl-2,4-decadienamide **10**,[5,6] pellitorine, isolated from the seeds of *Piper sylvaticum*.[1d,g]

The following procedure for the synthesis of dienamide **9** is representative.

The electrophilic substitution of the tributylstannyl group with iodine was performed by adding at 0 °C an ether solution (30 mL) of iodine (0.5 g, 2 mmol) to a solution of compound **1**[10,11] (0.85 g, 2 mmol) in 20 mL of Et_2O. After stirring for 1 h, the mixture was quenched with an aqueous solution (5%) of sodium thiosulfate and extracted with ether. The combined extracts were washed with water, dried over Na_2SO_4 and concentrated. The residue was treated with 50 mL of a half-saturated aqueous KF solution with vigorous shaking, and allowed to stand 15-30 min. The resulting white precipitate of tributyltin fluoride was removed by filtration; the organic

layer was separated and again washed with aqueous KF. After evaporation of the organic solvent, the crude product was distilled with a Kugelrohr apparatus (oven temp. 75 °C, 1 mbar) affording 0.36 g of compound **2** (72% yield).[11] A CH_2Cl_2 solution (15 mL) of freshly distilled S-phenyl carbonochloridothioate (0.3 g, 1.7 mmol) was added, under nitrogen, to a cold (0 °C) stirred suspension of anhydrous $AlCl_3$ (0.23 g, 1.7 mmol) in 15 mL of CH_2Cl_2. The resulting mixture was allowed to stir at 0 °C for 10 min. The obtained clear solution was transferred via syringe to the addition funnel of a three-necked flask, equipped with a magnetic stirrer, and cooled at 0 °C, under nitrogen, which contained a CH_2Cl_2 solution (15 mL) of compound **2** (0.36 g, 1.4 mmol). After complete addition at 0 °C, the mixture was stirred at the same temperature for 3 h and quenched with saturated aqueous NH_4Cl. After extraction with ethyl acetate, the organic extracts were washed with water, dried over Na_2SO_4 and concentrated. The product **3**[11] was isolated in 65% yield after flash chromatography (silica gel, petroleum ether:ethyl acetate 9:1). The thioester **3** was converted into the iodo-amide **5** following a reported procedure,[12] by adding silver trifluoroacetate (0.20 g, 0.9 mmol) to a stirred solution (25 mL) of the pyrrolidine (0.08 g, 1.1 mmol) and the thioester (0.29 g, 0.9 mmol) in THF at room temperature, under nitrogen, containing also powdered 4 A° molecular sieves. After 7 h, the reaction was worked up by removing the solvent in vacuo, resuspending the solid in ether, filtering and collecting the filtrate. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether:ethyl acetate 8:2), affording **5**[11] in 63% yield. The coupling reaction was performed by adding a 1 M THF solution (1 mL, 1 mmol) of pentylmagnesium bromide to a stirred suspension containing $NiCl_2$(dppe) (3 mol%) and the compound **5** (0.15 g, 0.54 mmol) in THF (30 mL) under nitrogen. After stirring for 5 h the mixture was quenched with NH_4Cl, extracted with ether, the extracts dried over Na_2SO_4 and, after evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether:EtOAc 8:2) leading to the product **9**[11] in 68% yield.

In conclusion, the procedure described here should provide a highly stereospecific route to various doubly stereodefined conjugated dienamides, starting from a common precursor. Moreover, taking into account the simplicity of the operations involved, we believe that the present method compares favourably with alternative methodologies.

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10. The starting diene **1** was synthesized by a selective coupling reaction as follows: a DMF solution (5 mL) of *E*-1,2-bis(tri-*n*-butylstannyl)ethene[13] (3.4 g, 5.6 mmol) was added, under nitrogen, to a solution of freshly distilled *E*-(2-bromovinyl)trimethylsilane (1 g, 5.6 mmol) and $PdCl_2(CH_3CN)_2$ (0.06 g, 0.23 mmol) in 5 mL of DMF. The mixture was stirred at room temperature and, after reaction completion (24 h), quenched with water and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and, after removal of the solvent by evaporation, the residue was taken up in a minimum of petroleum ether and passed through a short Florisil column, with petroleum ether as eluent, in order to remove the catalyst. Then the reaction mixture was worked up, as described above, with a half-saturated aqueous potassium fluoride solution. The residue was purified by distillation with a Kugelrohr apparatus (oven temp. 135 °C, 1 mbar) affording 1.34 g of the diene **1** (58% yield), (stereoisomeric purity *E,E/E,Z*=97/3, as evidenced by capillary GC analysis).
11. ^{1}H-NMR data were measured at 200 MHz and ^{13}C-NMR data at 50.3 MHz on a Varian XL 200, or on a Bruker AM 500, 500 MHz. GC/mass-spectrometry analysis were performed on a Hewlett-Packard 5890A GC equipped with HP-1 capillary column, 25 m, and HP MSD 5970B. **(1*E*,3*E*)-4-tri-*n*-butylstannyl-1-trimethylsilyl-1,3-butadiene 1**, ^{1}H-NMR data (500 MHz, $CDCl_3$): δ 0.08 (s, 9H), 0.7-1.7 (m, 27H), 5.80 (d, *J* = 17.7 Hz, 1H), 6.28 (d, *J* = 18.0 Hz, 1H), 6.48 (dd, *J* = 17.7, 9.4 Hz, 1H), 6.54 (dd, *J* = 18.0, 9.4 Hz, 1H) ppm. ^{13}C-NMR data (50.3 MHz, $CDCl_3$): δ -1.30, 9.48, 13.70, 27.29, 29.10, 132.60, 135.20, 146.90, 149.60. **(1*E*,3*E*)-4-iodo-1-trimethylsilyl-1,3-butadiene 2**, ^{1}H-NMR data (200 MHz, $CDCl_3$): δ 0.10 (s, 9H), 5.88 (d, *J* = 18.3 Hz, 1H), 6.42 (dd, *J* = 18.3, 10.1 Hz, 1H), 6.42 (d, *J* = 14.3 Hz, 1H), 7.07 (dd, *J* = 14.3, 10.1 Hz, 1H) ppm. MS: m/e 252 (M^+, 73), 237 (71), 211 (12), 185 (55), 171 (35), 125 (54), 110 (20), 109 (90), 97 (23), 95 (17), 83 (21), 73 (19), 59 (100). **Phenyl (2E,4E) 5-iodo-2,4-pentadienthioate 3**, ^{1}H-NMR data (500 MHz, $CDCl_3$): δ 6.50 (d, *J* = 14.6 Hz, 1H), 6.62 (dd, *J* = 14.5, 7.5 Hz, 1H), 7.16-7.30 (m, 2H), 7.32-7.48 (m, 5H) ppm. MS: m/e 316 (M^+, 32), 207 (100), 189 (52), 179 (39), 161 (13), 147 (17), 136 (55), 109 (19), 108 (24), 69 (15), 65 (14), 52 (33). **N-(5-iodo-2*E*,4*E*-decadienoyl)-pyrrolidine 5**, ^{1}H-NMR data (200 MHz, CD_3COCD_3): δ 1.75-2.00 (m, 4H), 3.38 (t, *J* = 6.8 Hz, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 6.45 (d, *J* = 15.1 Hz, 1H), 7.05 (d, *J* = 14.0 Hz, 1H), 7.08 (dd, *J* = 15.1, 11.2 Hz, 1H), 7.21-7.42 (m, 1H) ppm. MS: m/e 277 (M^+, 20), 207 (67), 179 (43), 150 (100), 122 (16), 81 (17), 70 (27), 52 (51). The spectra of dienamides **7-10** matched those previously reported.[1b,e,g,5]
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