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STEREOSELECTIVE PREPARATION OF CONJUGATED DIENOATES AND DIENAMIDES. NEW SYNTHESIS OF PELLITORINE AND PIPERCIDE.

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Abstract. (E) and (E,E)-conjugated dienoates and dienamides of high stereoisomeric purities are prepared via thermal SO_2 extrusion from cis-2,5-disubstituted-2,5-dihydrothiofene-1,1-dioxides generated by a retro Diels-Alder reaction. Applications of this method to the syntheses of two insecticidal natural dienamides : pellitorine and pipercide and of methyl tetradeca-2E,4,5-trienoate, an insect sex pheromone, are described.

Introduction

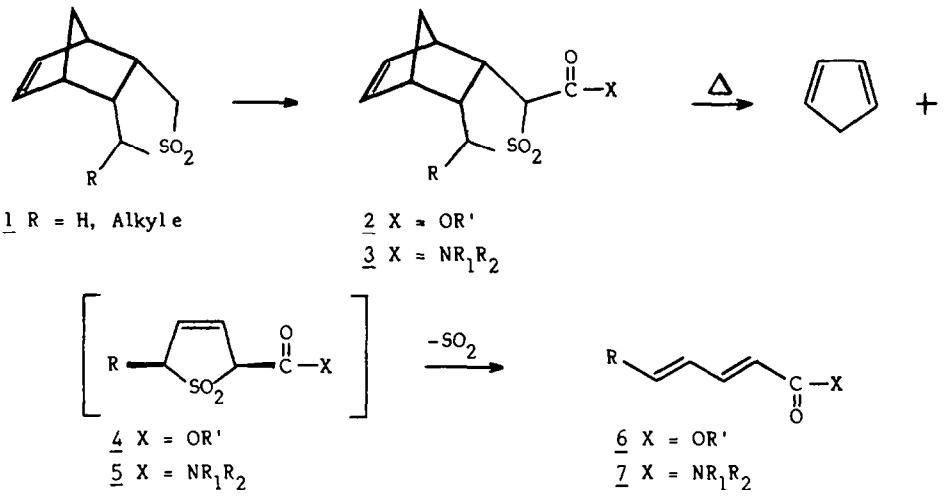
(2E,4E)-Dienamides constitute an important class of compounds occuring widely in a number of plants and showing interesting insecticidal activities [1]. They are accessible in only very small amounts from natural sources and therefore synthetic approaches to these rather unstable amides are required. Since (2E,4E)-dienoates are valuable intermediates for such purposes, much work has been devoted, over the past few years, to the stereoselective preparation of these species [2]. We recently described a stereoselective synthesis of (E)- and (E,E)-conjugated dienes which was applied to the obtention of some insect sex pheromones of high stereochemical purity [3]. This method has then been extended to the preparation of α-hydroxy conjugated dienes [4] and of conjugated dienones [5]. We report here that this process is quite general and can be useful for the selective synthesis of both conjugated (E)- and (E,E)-dienoates and dienamides.

Results and discussion

The thermal SO_2 extrusion from 2-alkyl- or cis-2,5-dialkyl-2,5-dihydrothiofene-1,1-dioxides (or sulfolenes) is a well known chelotropic reaction leading with high stereoselectivity (>99%) to (E)- or (E,E)-conjugated dienes, respectively [6]. (E)- and (E,E)-conjugated dienoates and dienamides 6 and 7 were obtained from the sulfolenes 4 and 5 generated by a retro Diels-Alder reaction of the α-carboxy-tricyclic sulfones 2 and 3 (scheme 1).

The action of ethyl chloroformiate with the lithium anion of the sulfones 1 was first considered for the preparation of 2 (X = OEt). However, in all cases, the yields were less than 50% and an important amount of starting material 1 was recovered. This reaction must be limited by the formation of an unreactive carbanion α to the carbethoxy and the sulfonyl groups and regeneration of half of the starting sulfone 1. A more general and effective procedure giving an easy access to either the sulfones 2 or 3 via the lithium carboxylates 8 is depicted in scheme 2.

Several sulfones 2 and 3 were thus obtained in a one pot reaction with fair to good yields as shown in the Table. In all cases, capillary gas chromatography coupled with mass spectrometry indicated the presence of a single stereoisomer arising probably from an attack of the electrophile from the less hindered exo face of the sulfonic five membered ring [3].



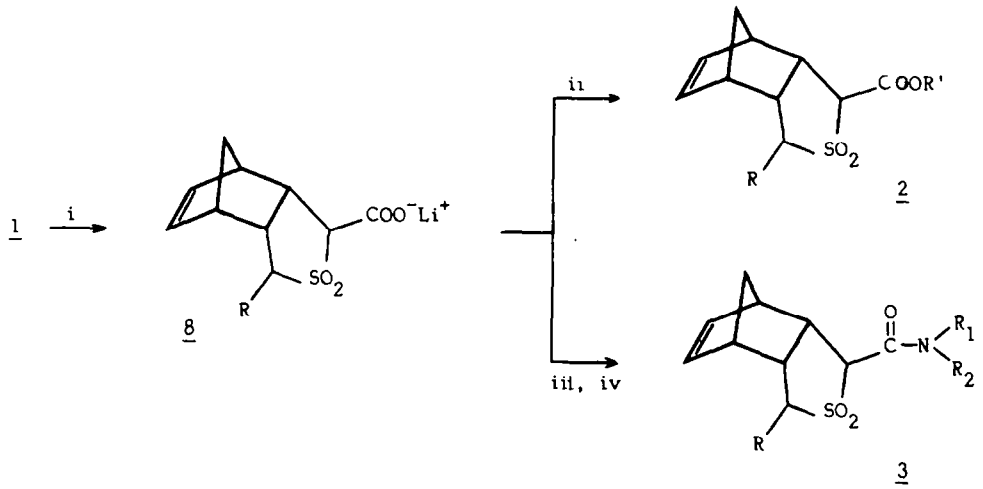
1 R = H, Alkyle

2 X = OR'
3 X = NR_1R_2

4 X = OR'
5 X = NR_1R_2

6 X = OR'
7 X = NR_1R_2

Scheme 1

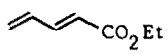
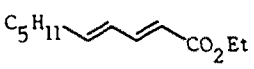
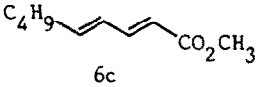
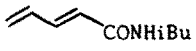
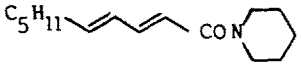
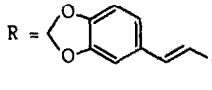


Scheme 2

i ; n-BuLi-THF, CO_2, -78°C ; ii : R'I, THF-HMPT (3 eq.), 20° ; iii : $(COCl)_2$, toluene, reflux ; iv : R_1R_2NH, 20°.

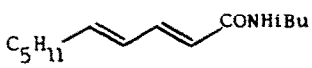
The thermolyses of sulfones 2a-c and 3a-b were carried out in vapor phase with short contact times (~50 ms) in an oven heated at 650°C, temperature necessary for a complete conversion. In such conditions, the intermediate sulfolenes 4 or 5 were entirely transformed with excellent yield and selectivity into the dienes 6a-c and 7a-b (see Table). The stereoisomeric purities of the latters were determined on the crude products by either ^{13}C or ^{1}H NMR for the terminal dienes 6a and 7a and by capillary gaz chromatography for the 4-alkyl dienoates or dienamides 6b-c and 7b-c. The E and E,E stereochemistry of the dienes were established by careful analyses of the ^{1}H NMR spectra : the values observed for vicinal coupling constants of vinylic protons (J = 15-16 Hz) were characteristic of trans double bonds.

Table. Stereoselective synthesis of (2E)- and (2E,4E)-dienoates and dienamides.

Starting sulfones 1	α- carboxy sulfones	Yield %[a]	Diene	Yield %[a]	Stereoisomeric purity
R = H	2a R' = C_2H_5	86	 6a	80	98[b]
R = C_5H_{11}	2b R' = C_2H_5	84	 6b	60	92[d]
R = C_4H_9	2c R' = CH_3	70	 6c	56	93[d]
R = H	3a R_1 = H, R_2 = iBu	52	 7a	67	95[c]
R = C_5H_{11}	3b R_1, R_2 = $-(CH_2)_5-$	40	 7b	75	96[d]
R = C_5H_{11}	3c R_1 = H, R_2 = iBu	52	7c	90	98[d]
	3d R_1 = H, R_2 = iBu	40	7d	75	95[c]

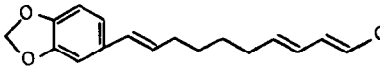
a) Isolated compounds purified by liquid chromatography ; b) Estimated by ^{13}C NMR ; c) Estimated by IH NMR ; d) Determined by gaz capillary chromatography.

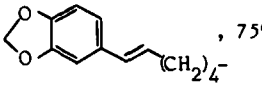
This general procedure was further extended to the stereocontrolled synthesis of three natural compounds presenting interesting biological properties : pellitorine, pipercide and methyl tetradeca-trans-2,4,5-trienoate.

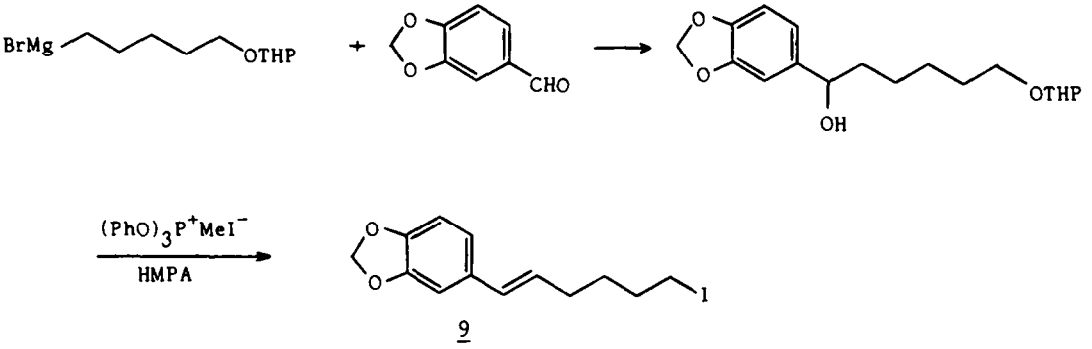
Synthesis of pellitorine  7c

Pellitorine is an insecticidal substance isolated from "Anacyclus Pyrethrum" roots and its structure was established as N-isobutyl (2E,4E)-decadienamide 7c[7]. Many reports on the synthesis of this dienamide have appeared in the literature [2a,b, 8] in general via (2E,4E)-decadienoic acid or its

esters. A straightforward way to pellitorine was developped through thermolysis of the sulfone 3c easily prepared from 1 (R = C_5H_{11}). In these conditions, pellitorine 7c was obtained with high stereoisomeric purity in 44% overall yield (see Table).

Synthesis of Pipercide  7d

Pipercide is another (2E,4E)-dienamide recently isolated from "Piper nigrum" and reported to show an insecticidal activity against the Adzuki bean-weevil [9]. Only one stereoselective synthesis of this interesting compound has been reported so far via the corresponding dienoate [10]. Our method allowed the direct obtention of the amide 7d : The anion of sulfone 1 (R = H) was reacted with the iodide 9 prepared from 1,5-pentanediol and piperonal [11] to give the sulfone 1 (R =  , 75% yield), which in the usual way led to the disubstituted sulfone 3d.

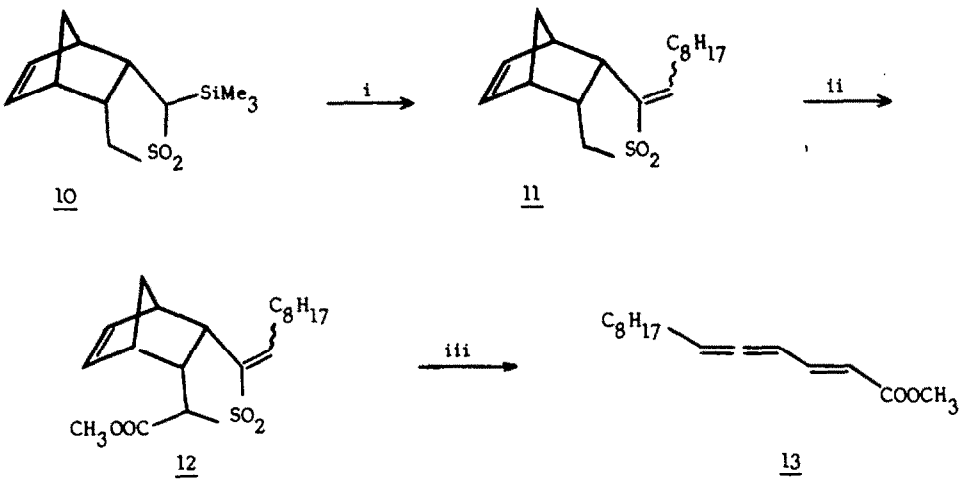


9

This sulfone was not volatile and the thermolysis, achieved by direct introduction in the hot zone (680-700°C) of the oven [12], afforded the all E-pipercide 7d with good yield and selectivity (see Table).

Synthesis of methyl tetradeca-2E,4,5-trienoate 13

Since its identification as the sex attractant of bean beetle "Acanthoscelides Obtectus", methyl tetradeca-2E,4,5-trienoate has been synthetized several times either in racemic [13] or in optically active form [14]. Our synthesis combined the procedures established for the preparation of vinylallenes [4] and dienoates as depicted in scheme 3.



10 11 12 13

i : n-BuLi, 20°C, n-$C_8H_{17}CHO$, 78% ; ii : n-BuLi, -78°C, CO_2 then CH_3I, 64% ; iii : 600°C, 25%

Scheme 3

This quite short synthesis suffered however from the low thermolysis yield owing to the thermal fragility of both the sulfone 12 and the triene 13.

Experimental

IR spectra were recorded on a Perkin-Elmer 682 spectrometer. N.M.R. spectra were recorded at 90 MHz on a Perkin-Elmer R-32 or at 250 MHz on a Brucker AM 250. Mass spectra were established on a GC/MS Hewlett-Packard 5992A or on a GC/MS Ribermag R-10-10 instrument. Melting point were determined with a Mettler FP-51 apparatus and are uncorrected. Flash thermolyses were carried out with an apparatus similar to the one described previously (15). Sulfones 1 and 10 were prepared as reported (5).

Preparation of sulfones 2 and 3 : General procedure

Butyllithium (1.6 M in hexane, 3.45 ml, 5.5 mmoles) was added to a stirred solution of the suitable sulfone 1 (5 mmoles) in dry THF (10 ml) under N2 at -78°C (dry ice-acetone). Dry gazeous CO2 was bubbled in the solution for 1 h at -78°C and for 1 h at room temperature. Two different ways were then followed :

- A solution of alkyl halide (15 mmoles) and dry HMPA (15 mmoles) in dry THF (5 ml) was added and the reaction mixture was stirred for 15 h at room temperature. Water (15 ml) was added and the aqueous phase was extracted with ether (3 x 15 ml). The combined ether extracts were dried (MgSO4) and concentrated in vacuo and the crude products were chromatographed (70/30 hexane/ethyl acetate) to provide the sulfones 2.

- The solution was concentrated in vacuo and the residue was dissolved in dry toluene (20 ml). Oxalyl chloride (7 mmoles) was added dropwise and the solution was refluxed for one hour. After cooling to room temperature, the required amine (10 mmoles) was added and the reaction mixture was stirred for 15 h at room temperature. After addition of water (15 ml) the aqueous phase was extracted with ether (3x15 ml). The ether extracts were dried (MgSO4) and concentrated in vacuo. The crude products were purified by flash chromatography on silica gel (70/30 hexane/ethyl acetate) to give the desired sulfones 3.

2a : yield 86% ; mp 102°C ; spectral data are identical with the one described (5).

2b : yield 84% ; oil ; IR (CDCl3) 3060, 1740, 1300, 1140 cm-1 ; NMR (CDCl3) δ0.95 (br.t, 3H), 1.35 (t, J = 7 Hz, 3H), 1.25 - 2.0 (m, 10H), 2.4 (m, 2H), 3.35 (m, 4H), 4.3 (q, J = 7 Hz, 2H), 6.3 (s, 2H). MS : m/e 326 (M+, 1.5), 281 (2), 261 (26), 197 (36), 66 (100). Anal. calcd for C17H26O4S : C, 62.55 ; H, 8.03 ; S, 9.82. Found C, 62.46 ; H, 8.17 ; S, 9.90.

2c : yield 70% ; oil ; IR (CDCl3) 3060, 1745, 1300, 1145 cm-1 ; NMR (CDCl3) δ0.95 (br.t, 3H), 1.2-1.8 (m, 8H), 2.4 (m, 2H), 3 - 3.25 (m, 4H), 3.85 (s, 3H), 6.3 (br.s, 2H) ; MS : m/e 298 (M+, 2.1), 253 (3), 233 (23), 66 (100).

3a : yield 52% ; mp 129°C ; IR (CDCl3) 3420, 3060, 1680 cm-1 ; NMR (CDCl3) δ0.9 (d, J = 7 Hz, 6H), 1.2 - 1.9 (m, 5H), 2.8 - 3.4 (m, 7H), 6.3 (m, 3H) ; MS : m/e 283 (M+, 7), 268 (7), 240 (16), 211 (30), 66 (100) ; Anal. calcd for C14H21NO3S : C, 59.34 ; H, 7.47 ; N, 4.94 ; S, 11.32 ; Found : C, 59.56 ; H, 7.32 ; N, 4.81 ; S, 11.53.

3b : yield 40% ; mp 171°C ; IR (CDCl3) 3060, 1650, 1300, 1140 cm-1 ; NMR (CDCl3) δ 0.9 (br.t, 3H), 1.2 - 1.9 (m, 16H), 2.45 (m, 2H), 3.0 (m, 2H), 3.2 - 4 (m, 6H), 6.3 (s, 2H) ; CIMS : m/e 366 (M^++1, 100), 365 (M+, 5), 301 (22), 236 (25) ; Anal. Calcd for C20H31NO3S : C, 65.71 ; H, 8.55 ; N, 3.83 ; S, 8.77; Found : C, 65.60 ; H, 8.43 ; N, 4.10 ; S, 8.79.

3c : yield 52% ; mp 126°C ; IR (CDCl3) 3420, 3060, 1685 cm-1 ; NMR (CDCl3) δ 0.8 - 1.1 (m, 3H), 0.94 (d, J = 7 Hz, 6H), 1.2 - 2.0 (m, 11H), 2.45 (m, 2H), 3.0 - 3.4 (m, 4H), 4.3 (m, 2H), 6.3 (s, 2H), 7.3 (br.t, 1H) ; CIMS : m/e 354 (M^++1, 100) 353 (M+, 19) ; Anal. calcd for C19H31NO3S : C, 64.55 ; H, 8.84 ; N, 3.96 ; S, 9.07 ; Found : C, 64.02 ; H, 8.82 ; N, 4.40 ; S, 8.90.

3d : yield 41% ; mp 136°C ; IR (CDCl3) 3420, 3060, 1680, 1300, 1140 cm^{-1} ; NMR (CDCl3) δ 0.95 (d, J = 7 Hz, 6H), 1.3 - 2.4 (m, 13H), 2.8 - 3.4 (m, 6H), 5.9 (s, 2H), 6.05 - 6.5 (m, 5H), 6.75 (s, 2H), 6.85 (s, 1H) ; CIMS : m/e 486 (M^++1 100), 485 (M+, 68) ; Anal. calcd for C27H35NO5S : C, 66.70 ; H, 7.27; N, 2.88 ; S, 6.60 ; Found : C, 66.0 ; H, 7.22 ; N, 3.00 ; S, 6.20.

Sulfone 11

To a stirred solution of 10 (1.28 g, 5 mmoles) in dry THF (10 ml), kept at room temperature under N2, was added dropwise 3.45 ml (5.5 mmoles) of n-BuLi 1.6 M in hexane. After 15 minutes the solution was cooled to -78°C and nonanal (752 mg, 6 mmoles) was added dropwise. The reaction mixture was allowed to warm to room temperature and water (15 ml) was added. After ether extraction (3x15 ml), the organic phase was dried (MgSO4) and concentrated in vacuo. Flash chromatography on silica gel (hexane/ethyl acetate 75/25) provided 1.12 g (73%) of 11 as a mixture of 2 isomers which were not separated.
IR (CDCl3) 3060, 1670, 1300, 1140 cm-1 ; NMR (CDCl3) δ 0.9 (br.t, 3H), 1.1 - 1.8 (m, 14H), 2.3 - 2.9 (m, 3H), 2.95 - 3.4 (m, 5H), 5.8 - 6.3 (m, 3H) ; MS : m/e 243 (25), 66 (100).

Sulfone 12

As described in the general procedure (see above), 900 mg of 11 gave 684 mg (64%) of the sulfone 12 as a mixture of two stereoisomers.
IR (CDCl3) 3060, 1730, 1670, 1300, 1140 cm-1 ; NMR (CDCl3) δ 0.90 (br.t, 3H), 1.2 - 1.8 (m, 14H), 2.2 - 2.4 (m, 2H), 3.1 - 3.6 (m, 5H), 3.8 (s, 3H), 6.2 (br.s, 2H), 6.35 - 6.55 (m, 1H) ; MS : m/e 301 (39), 66 (100) ; Anal. calcd for C20H30O4S : C, 65.54 ; H, 8.25 ; S, 8.75 ; Found : C, 65.78 ; H, 8.22 ; S, 8.62.

General procedure for thermolyses

Small samples (200 to 500 mg) of sulfones 2 or 3 were evaporated through an horizontal mullite tube (15) (650°C, 1 - 3 x 10-2 torr) and the products were collected in a trap cooled by liquid nitrogen. After warming to room temperature the content of the trap was dissolved in ether and the resulting solution was evaporated under reduced pressure. The residue was purified by chromatography (silica gel, hexane/ether) to provide pure dienes 6 or 7.

The thermolysis of 2a ⟶ 6a has already been described [5].

Ethyl (2E,4E)-decadienoate 6b

490 mg of sulfone 2b were thermolysed to give 176 mg (60%) of the dienoate 6b. Its spectral data were identical with those reported (16).

Methyl (2E,4E)-nonadienoate 6c

270 mg of sulfone 2c gave 85 mg (56%) of the ester 6c. IR (neat) 1725, 1645, 1620 cm-1; NMR (CDCl3) δ 1.0 (t, J = 7 Hz, 3H), 1.1 - 1.6 (m, 4H), 2.2 (m, 2H), 3.7 (s, 3H), 5.78 (d, J = 16 Hz, 1H), 6.15 (td, J = 15 Hz, 7 Hz, 1H), 6.25 (dd, J = 15 Hz, 10 Hz, 1H), 7.25 (dd, J = 16 Hz, 10 Hz, 1H) ; MS : m/e 168 (M+, 37), 153 (2), 137 (24), 111 (100).

N-isobutyl (2E,4)-pentadienamide 7a

195 mg of sulfone 3a gave 72 mg (67%) of the amide 7a. IR (CDCl3) 3460, 3300, 3080, 1680, 1630, 1600 cm-1 ; NMR (CDCl3) δ 0.95 (d, J = 7 Hz, 6H), 1.86 (m, 1H), 3.15 (t, J = 7 Hz, 2H) ; 5.3 - 5.6 (m, 2H), 6.18 (d, J = 15 Hz, 1H), 6.2 - 6.60 (m, 1H), 7.12 (dd, J = 16 Hz, 10 Hz, 1H), 7.88 (br.t, 1H); MS : m/e 153 (M+, 15), 110 (14), 81 (100).

N,N-pentamethylene (2E,4E)-decadienamide 7b

400 mg of sulfone 3b gave 194 mg (75%) of dienamide 7b as an oil.
IR (CDCl3) 1655, 1630, 1605 cm-1 ; NMR (CDCl3) δ 0.95 (t, J = 7 Hz, 3H), 1.2 - 1.7 (m, 12H), 2.15 (m, 2H), 3.5 (m, 4H), 6.05 (dt, J = 16 Hz, 7 Hz, 1H), 6.15 (dd, J = 16 Hz, 11 Hz, 1H), 6.3 (d, J = 15 Hz, 1H), 7.15 (dd, J = 15 Hz, 11 Hz, 1H) ; MS : m/e 235 (M+, 60), 220 (5), 206 (18), 192 (86), 84 (100) ; Anal. calcd for C15H25NO : C, 76.54 ; H, 10.71 ; N, 5.95 ; Found : C, 76.62 ; H, 10.83 ; N, 6.12.

N-isobutyl (2E,4E)-decadienamide or pellitorine 7c

300 mg of sulfone 3c gave 170 mg (90%) of 7c : mp : 86°C ; lit (7) 90°. The spectral data were in good agreement with the reported values (8).

Pipercide 7d

256 mg of sulfone 3d were introduced directly with a spatula in an oven heated at 680°C under reduced pressure (10-5 torr). The oven was then cooled to room temperature and the solid product formed was recovered by washing the walls with ether. Concentration in vacuo gave crude 7d which was purified by chromatography (silica gel ; 60/40 hexane/ethyl acetate) to afford 140 mg (75%) of pipercide : mp = 116°C ; lit (10) 120°C. Good agreement was observed between the spectral data and those reported (10).

Methyl (2E,4,5)-tetradecadienoate 13

290 mg of sulfone 12 thermolyzed in the usual way at 600°C gave 140 mg of crude dienoate which was purified by flash chromatography on silica gel (90/10 hexane/ether) to give 47 mg (25%) of pure 13. IR, NMR and MS were identical with those described (13d).

Acknowledgement. We are indebted to Dr. J.L. Ripoll for his valuable assistance in the thermolysis of 3d and to Prof. L. Crombie for sending us NMR spectra of pipercide 7d.

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11) Iodide 9 was prepared according to a method developped by Crombie for the preparation of analogous iodides (10).
12) These thermolyses have been carried out with the help of Dr. J.L. Ripoll (Université de Caen), the instigator of this useful technics.
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