Table 3. Stereochemistry of 2-(3′-Alkenyl)-1,3-dithianes **6**[a]

Product	Isomer[b]	^{13}C-NMR ($CDCl_3$/TMS) δ(ppm)[c]		Z/E-Ratio[d] (%)
		=CH–$\underline{C}H_2$	R^2 or R^3	
6b	*Z*	22.72 (23.20)	20.57 (20.98) ($\underline{C}H_2$)	95
	E	–[e] (28.68)	25.59 (26.06) ($\underline{C}H_2$)	5
6c	*Z*	24.22 (22.85)		95
	E	28.47 (28.66)		5
6e	*Z*	22.02 (22.38)	20.39 (20.87) ($\underline{C}H_2$)	95
	E	27.10 (27.89)	25.55 (25.95) ($\underline{C}H_2$)	5
6f	*Z*	23.45 (22.03)		95
	E	28.28 (27.87)		5
6h	*Z*	24.59 (25.53)	25.64 (24.69) ($\underline{C}H_3$)	95
	E	24.41 (19.72)	15.88 (19.45) ($\underline{C}H_3$)	5
6k	*Z*	23.90 (24.74)	25.50 (24.51) ($\underline{C}H_3$)	95
	E	23.68 (18.90)	–[e] (19.29) ($\underline{C}H_3$)	5

[a] For R^1, R^2 and R^3, see Table 2.
[b] Identification of *Z*- and *E*-isomers are carried out on the basis of the chemical shift of the allylic carbons[13]; for compounds **6h** and **6k**, the identification is also corroborated by ^{1}H-NMR, using an empirical formula[14] to calculate the vinylic proton chemical shift: from these calculations, the *E*-isomer may be attributed to the most deshielded peak and the *Z*-isomer to the least deshielded one.
[c] Calculated values are given in parenthesis.
[d] The *Z*/*E*-ratio [(±) 3%] are determinated by HPLC and GC analysis.
[e] Undetected.

1,3-Dithianes 6; General Procedure:
To a solution of potassium *tert*-butoxide (1.12 g, 10 mmol) in dry ether (120 ml) is added phosphonium salt **4** (11 mmol) under nitrogen atmosphere. After stirring for 15 min the carbonyl compound **5** (10 mmol) is added. The mixture is stirred for 4 h, and hydrolysed with a 1 normal solution of hydrobromic acid (5 ml), the etheral layer is washed with water (3 × 15 ml), dried with sodium sulfate and the solvent is removed in vacuum. The residual oil is purified by column chromatography on silica gel (20 g silica gel for 1 g oil) using gradient of hexane/dichloromethane as eluent.

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N^1-Alkylation of Dihydrolysergic Acid

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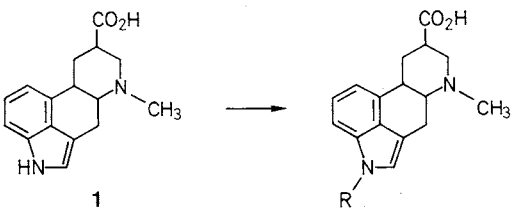
A new procedure for alkylating dihydrolysergic acid (**1**) on the indole nitrogen is reported. Previous procedures involved reaction of the indoyl anion with an alkyl halide. As the alkyl group gets larger, dehydrohalogenation of the alkyl halide becomes the preferred reaction and little or no N^1-alkylation occurs. By using alkyl tosylates in place of alkyl halides, we have been able to alkylate **1** on the indole nitrogen with a wide variety of alkyl groups in high yield.

N^1-Alkyl derivatives of dihydrolysergic acid (**1**) have been shown to be useful intermediates in the synthesis of serotonin antagonists,[1,2] prolactin inhibitors,[3] and dopaminergic agents.[4] Because of the difficulty in adding larger groups to the indole nitrogen, structure-activity relationship (SAR) studies have generally been limited to substitution by alkyl groups containing one to three carbons or by benzyl groups. While there are a large variety of substitution reactions reported[5–12] for alkylation of indoles, they are most successful when used with small alkylating agents that do not undergo competitive elimination reactions. We wish to report new conditions that allow alkylation of **1** on the indole nitrogen with most any alkyl group in high yield.

Previously reported procedures,[1,3] for N^1-alkylation of **1** generated the indoyl anion with either sodium amide in liquid ammonia or potassium hydroxide in dimethylsulfoxide solution followed by addition of an alkyl halide. These conditions are also very favorable for dehydrohalogenation of the alkyl halide to form the corresponding olefin. As the alkyl group becomes larger, dehydrohalogenation becomes the preferred reaction and little or no N^1-alkylation occurs. We found that improved yields of alkylated product could be obtained from a potassium hydroxide/dimethyl sulfoxide solution of **1** by using alkyl tosylates in place of alkyl halides. Changing the leaving group minimized the competing elimination reaction allowing substitution to occur in high yield. A comparison of the literature procedures with our procedure is made in Table 1.



1 **2**

Table 1. Comparison of Different Alkylation Procedures for the Conversion of **1** → **2**

R in **1**, **2**		NH_3/Na/ RI(Br)[a]	DMSO/ KOH/RBr[b]	DMSO/ KOH/ROTs[c]
		Yield (%)	Yield (%)	Yield (%)
a	i-C_3H_7	81	86	91
b	i-C_4H_9	61 (Br)	94	94
c	s-C_5H_{11}	< 10	32	92
d	cyclopentyl	–[d]	69	91
e	cycloheptyl	–[d]	–[d]	93
f	cyclopropylmethyl	–[d]	–[d]	87[e]
g	n-C_8H_{17}	–[d]	–[d]	77[f]

[a] 4 Equivalent of the alkylating reagent was used.
[b] 3 Equivalent of the alkylating reagent was used.
[c] 1.3–1.6 Equivalent of the alkylating reagent was used.
[d] Reaction not carried out.
[e] Tosylate had to be prepared fresh prior to use.
[f] Recrystallization from acetone/methanol required for acceptable purity, hence the lowered yield.

The alkylation reaction is most effectively carried out by dissolving **1** in dimethyl sulfoxide in the presence of excess (5–6 equiv.) potassium hydroxide, followed by addition of the appropriate tosylate, either neat or as a solution in dimethyl sulfoxide, over an hour's time. The reaction is quicker if powdered potassium hydroxide is used, but equivalent results are obtained with pelletized potassium hydroxide. Less base can be used as well, but this also slows the reaction. When sodium hydroxide is used as base, yields drop somewhat. Lithium hydroxide gives very low yields of product. Other polar, aprotic solvents such as dimethylformamide, dimethylacetamide, or *N*-methyl-2-pyrrolidone are not as useful since they will react with the potassium hydroxide over time. All reactions were run at room temperature. No epimerization at the C-8 carbon α- to the carbonyl group was observed in any of the reactions.

Not all the alkylations attempted were successful. Reaction of **1** with neopentyl tosylate gave no alkylated product. Alkylation of **1** with cyclohexyl tosylate was only partially successful (~ 20% theory yield) even when large excesses (3–4 equiv.) of cyclohexyl tosylate were used. Apparently, in the case of cyclohexyl tosylate, the competing elimination reaction is much faster than the substitution reaction.[13] Most surprisingly, reaction of either

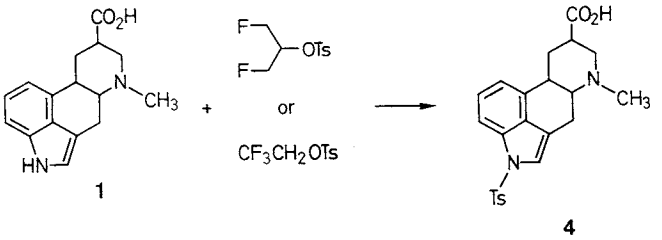
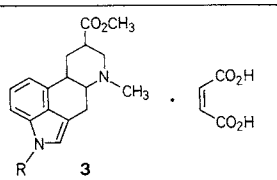


Table 2. Physical and Spectral Data of Compounds **2** and **3** Prepared

Product	^{1}H-NMR (CD_3COOD/TMS)[a] δ (ppm)	MS[b] m/e (M^+, 100%)	Product[c]	m.p. (°C)[d] (solvent)	Molecular Formula[e] or Lit. m.p. (°C)
2a	1.55 (dd, 6H, J = 7 Hz); 1.85 (q, 1H, J = 14 Hz); 3.15 (m, 7H); 4.0 (m, 1H); 4.75 (sept, 1H, J = 7 Hz); 6.95 (d, 1H, J = 7 Hz); 7.05 (s, 1H); 7.18 (t, 1H, J = 7 Hz); 7.25 (d, 1H, J = 7 Hz)	312	**3a**	109–110[f] (CH_3OH/H_2O)	110–114[16]
2b	0.9 (d, 6H, J = 6 Hz); 1.75 (q, 1H, J = 13 Hz); 2.15 (sept, 1H, J = 6 Hz); 3.20 (m, 7H); 3.55 (m, 3H); 3.90 (d, 2H, J = 6 Hz); 4.0 (s, 1H); 6.95 (m, 2H); 7.28 (m, 2H)	326	**3b**	143–145 (CH_3OH/Ether)	$C_{25}H_{32}N_2O_6$ (456.5)
2c	0.80 (m, 6H); 1.75–2.0 (m, 5H); 3.25 (m, 7H); 3.55 (m, 3H); 4.05 (m, 2H); 6.95 (d, 1H, J = 3 Hz); 7.05 (s, 1H); 7.18 (t, 1H, J = 6 Hz); 7.25 (d, 1H, J = 9 Hz)	340 (M^+, 10%) 341 (M + 1, 100%)	**3c**	162–163 (CH_3OH/Ether)	$C_{26}H_{34}N_2O_6$ (470.6)
2d	1.7–2.2 (m, 9H); 3.15 (m, 7H); 3.55 (m, 3H); 4.0 (m, 1H); 4.78 (q, 1H, J = 6 Hz); 6.95 (d, 1H, J = 7 Hz); 7.05 (s, 1H); 7.18 (t, 1H, J = 7 Hz); 7.25 (d, 1H, J = 7 Hz)	338	**3d**	177.5–178 (C_2H_5OAc/Ether)	$C_{26}H_{32}N_2O_6$ (468.6)
2e	1.6–2.1 (m, 13H); 3.15 (m, 7H); 3.55 (m, 3H); 4.0 (m, 1H); 4.4 (q, 1H, J = 3 Hz); 6.95 (d, 1H, J = 7 Hz); 7.07 (s, 1H); 7.18 (t, 1H, J = 7 Hz); 7.25 (d, 1H, J = 7 Hz)	366	**3e**	193–195 (CH_3OH/Ether)	$C_{28}H_{36}N_2O_6$ (496.6)
2f	0.4 (m, 2H); 0.6 (m, 2H); 1.3 (m, 1H); 1.8 (q, 1H, J = 14 Hz); 3.2 (m, 7H); 3.6 (m, 3H); 4.0 (d, 3H, J = 7 Hz); 6.95 (d, 1H, J = 3 Hz); 7.05 (s, 1H); 7.18 (t, 1H, J = 5 Hz); 7.25 (d, 1H, J = 7 Hz)	324	**3f**	155–156 (CH_3OH/Ether)	$C_{25}H_{30}N_2O_6$ (454.5)
2g	0.9 (t, 3H, J = 7 Hz); 1.3 (m, 10H); 1.8 (m, 3H); 3.15 (m, 7 H); 3.55 (m, 3H); 4.0 (m, 1H); 4.1 (t, 2H, J = 7 Hz); 6.95 (d, 2H, J = 3 Hz); 7.2 (m, 2H)	382	**3g**	64.5–66 (C_2H_5OAc/Hexane)	$C_{29}H_{40}N_2O_6$ (512.7)

[a] Recorded on a GE QE-300 spectrometer.
[b] Obtained on a CEC-21-110 Mass spectrometer.
[c] Maleic acid salt of the ester of **2a–g**.
[d] Measured on a Thomas-Hoover capillary melting point apparatus.
[e] Satisfactory microanalyses obtained: C ±0.28, H ±0.26, N ±0.23.
[f] Free base.



1,1,1-trifluoroethyl tosylate or 1,3-difluoro-2-propyl tosylate with **1** yielded **4** rather than the desired fluoroalkylated product.

Because of the hygroscopic nature of the N^1-alkylated dihydrolysergic acids, satisfactory elemental analysis could not be obtained on the free acids. The alkylated products were identified by mass spectroscopy and ^{1}H-NMR data and characterized as the methyl ester. This data is presented in Table 2. Purity of the free acids was determined by HPLC analysis and Karl Fischer titration.

Both dimethyl sulfoxide and potassium hydroxide were reagent grade and were used as purchased. Dihydrolysergic acid (**1**) was purchased from Gideon-Richter, Ltd. and assayed by HPLC to be 100% pure (calculated on the dried substance). Water content of **1** was determined to be 8.5% by Karl Fischer titration (KF) using a Fischer Automatic K-F Titrimeter® system. HPLC analysis of **1** and alkylated products was carried out using a Zorbax CN HPLC column (mobile phase: 75/25 0.1 molar ammonium acetate/acetonitrile, flow rate at 2 ml/min) on a Waters M-45 liquid chromatograph pump with a Waters 440 absorbance detector set at 254 nm. Melting points are uncorrected. Running the reactions under a nitrogen atmosphere was not necessary for the success of the reaction. The alkyl tosylates used were prepared using standard literature procedures[14,15] and were satisfactorily characterized prior to use.

(8β)-1-Cyclopentyl-6-methylergoline-8-carboxylic Acid (2d); Typical Procedure:

A mixture of **1** (10 g, 33.88 mmol), powdered potassium hydroxide (86% pure, 12.05 g, 185 mmol) and dimethyl sulfoxide (75 ml) is stirred until all **1** dissolves, then a solution of (12.21 g, 50.81 mmol) cyclopentyl tosylate in dimethyl sulfoxide (25 ml) is added dropwise over a 2 h period. After 2 h, the reaction is poured into ice water (500 ml) and filtered to remove turbidity. The product is precipitated from the filtrate by adjusting the pH to 5–6 with glacial acetic acid, then collected and dried *in vacuo*; yield: 11.43 g (assay 92.5%, KF = 0.9%, % theory yield 91%). Purer material can be obtained if necessary by reprecipitating the product from dilute ammonia solution.

MS (70 eV): m/e = 338(100%).

^{1}H-NMR (CD_3COOD): δ = 1.7–2.2 (m, 9H); 3.15 (m, 7H); 3.55 (m, 3H); 4.0 (m, 1H); 4.78 (quint, 1H, J = 6 Hz); 6.95 (d, 1H, J = 7 Hz); 7.05 (s, 1H); 7.18 (t, 1H, J = 7 Hz); 7.25 ppm (d, 1H, J = 7 Hz).

The elemental analysis is carried out on the maleic acid salt **3d** of the methyl ester of **2d**.

$C_{26}H_{32}H_2O_6$	calc.	C 66.65	H 6.88	N 5.98
(468.6)	found	66.43	6.95	6.20

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Reaction of Ethyl (*E*)-3-Methoxy-2-butenoate with Some Substituted Aromatic Aldehydes: Synthesis of 5-Aryl-3-Methoxy-(2*E*,4*E*)-2,4-Pentadienoic Acids

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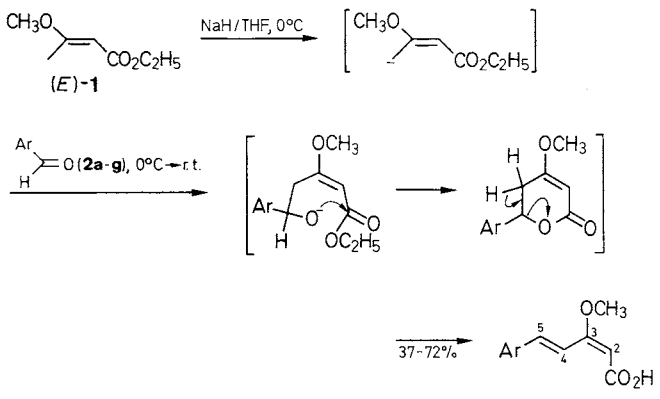
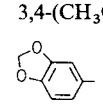
The reaction between ethyl (*E*)-3-Methoxy-2-butenoate (**1**) and some substituted benzaldehydes **2** in the presence of sodium hydride leads to 5-aryl-3-methoxy-(2*E*,4*E*)-*2,4-pentadienoic acids* **3**. The UV,IR and ^{1}H- and ^{13}C-NMR spectral data for the compounds synthesized are presented and discussed.

As part of our study on the synthesis of some naturally occurring butenolides[1] and pyrones[2] we have now investigated the synthesis of some 5-aryl-3-methoxy-(2*E*,4*E*)-2,4-pentadienoic acids **3** and their subsequent cyclization reactions.

Although a great deal of work concerning the synthesis of 3-alkoxy-dienoic acids has been published,[2–6] little is known about the synthesis of these acids from ethyl (*E*)-3-methoxy-2-butenoate.

In the preceding paper[2] we described the synthesis of 6-aroyl-5-aryl-3-methoxycyclohex-2-enones from the reaction of α,β-unsaturated carbonyl compounds with ethyl (*E*)-3-methoxy-2-butenoate (**1**). Thus it became of interest to examine the reaction of **1** with aromatic aldehydes. Condensation of **1** in tetrahydrofuran at 0 °C with aromatic aldehydes **2** in the presence of sodium hydride led to 5-aryl-3-methoxy-(2*E*,4*E*)-2,4-pentadienoic acids **3a–g** presumably through 2-oxo-5,6-dihydro-2*H*-pyrans as intermediate in the reaction[4–6] (Table 1). These intermediates were not isolated but they could proposed as mentioned previously[4–6] (Scheme **A**).



2, 3	Ar	2/3	Ar
a	C_6H_5	**e**	2-naphthyl
b	$4\text{-}CH_3OC_6H_4$	**f**	$2,6\text{-}Cl_2C_6H_3$
c	$3,4\text{-}(CH_3O)_2C_6H_3$	**g**	$3,4\text{-}Cl_2C_6H_3$
d			

Scheme **A**

The 2*E*,4*E*-configuration was assigned to compounds **3a–g** by analysis of their ^{1}H-NMR data (Table 1).