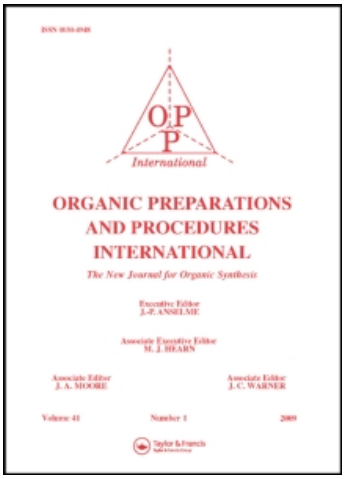

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BUILDING BLOCKS FOR THE SYNTHESIS OF MAYTANSINOIDS

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BUILDING BLOCKS FOR THE SYNTHESIS OF MAYTANSINOIDS

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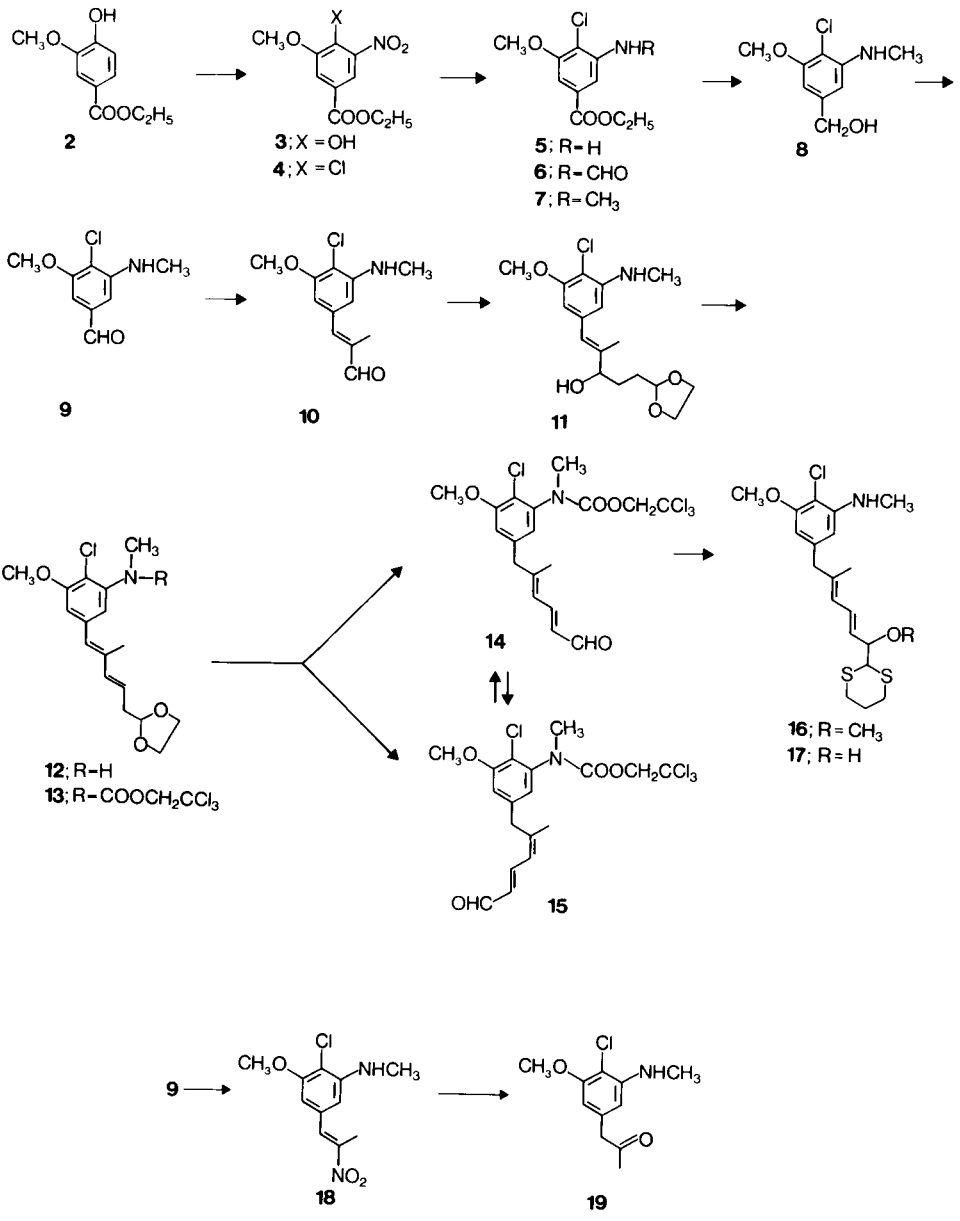
Some time ago we described in a preliminary communication [1] synthetic routes to compounds 14 and 19 which are potential building blocks for the synthesis of maytansinoids, e.g. maytansine (1). We now disclose the experimental details of our work summarized in the Scheme on the next page. Recently an analogue of the dienal 14, [2] prepared by another synthetic pathway via 8, [2] has been successfully elaborated to (±)-N-methylmaysenine. [3] Alternative syntheses have also been published for intermediate 7 [4] and for the corresponding methyl ester. [5]

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Beckman IR 9, relevant bands are indicated in cm^{-1}. UV spectra were obtained in ethanol on a Beckman Acta III, λ max are indicated in nm (ε). NMR spectra were recorded in $CDCl_3$ on a Varian A-60D or a Bruker HX-270. Chemical shifts are indicated in ppm with TMS as internal standard. ^{13}C NMR were recorded on a Bruker HX-270. MS were performed on a MS 9 or MS 902-DS30 (high resolution spectra, M = molecular ion). Relevant peaks are given in m/e (rel. int. in %). Column chromatography was carried out on silical gel Merck (70-230 mesh).



Ethyl 4-hydroxy-3-methoxy-5-nitrobenzoate (3).- To a stirred solution of 98 g (0.50 mol) of ethyl vanillate (2) [6] in 500 ml glacial acetic acid was added at once 500 ml of 8 % aq. HNO_3. After 5 min. crystals began to form and the reaction became exothermic. The reaction medium was cooled to 10° with an ice bath and held at this temperature for an additional 10 min. Then 500 ml of water were added and the crystals were collected and washed with 500 ml of water. The white crystals were dried to give 90 g (75 %) of 3, mp. 122-124°.

IR (KBr): 3278, 1718; NMR: δ 1.43 (t, J = 7 Hz, 3H), 4.02 (s, 3H), 4.42 (q, J = 7 Hz, 2H), 7.79 (d, J = 2 Hz, 1H), 8.48 (d, J = 2 Hz, 1H), 11.09 (s, 1H); MS: 241 (70, M).

Anal. Calcd. for $C_{10}H_{11}NO_6$: C, 49.80; H, 4.60; N, 5.81 %
Found: C, 50.03; H, 4.56; N, 5.79 %

Ethyl 4-chloro-3-methoxy-5-nitrobenzoate (4).- To a stirred solution of 241 g (1 mol) of 3 and 42.5 g (1 mol) of LiCl in 4 l of DMF was added in one portion 400 ml of $POCl_3$; the temperature rose to 50°. Then 121 g (1 mol) of s-collidine was added and the reaction temperature was kept at reflux for 2 hrs. The reaction mixture was poured onto ice and the aqueous phase was extracted three times with 1 l of ether. The organic phase was washed twice with 200 ml of water, five times with 200 ml of a saturated aq. $NaHCO_3$ solution, twice with 200 ml of water and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the crystalline residue was recrystallized from ether to yield 190 g (73 %) of 4, mp 93-95°.

IR (KBr): 1723; NMR δ 1.43 (t, J = 7 Hz, 3H), 4.08 (s, 3H), 4.46 (q, J = 7 Hz, 2H), 7.84 (d, J = 2 Hz, 1H), 8.10 (d, J = 2 Hz, 1H); MS: 259 (80, M, Cl).

Anal. Calcd. for $C_{10}H_{10}ClNO_5$: C, 46.26 H, 3.88 N, 5.39 Cl, 13.65 %
Found: C, 46.26 H, 3.83 N, 5.17 Cl, 13.30 %

Ethyl 3-amino-4-chloro-5-methoxybenzoate (5)

a) Reduction of 4 with Zn/Acetic acid.- A mixture of 1.3 l glacial acetic acid and 200 g Zn powder was heated to 70° with stirring. Then 200 ml of a solution of 260 g (1 mol) of 4 in 4 l of glacial acetic acid was added in one portion. Heating was discontinued and the rest of the solution added over a period of 1 hr. After the addition was complete, the reaction mixture was filtered and the collected solid washed several times with 250 ml of acetic acid. The filtrate was evaporated under vacuum and 1 l of water was added to the residue. The aqueous phase was made alkaline with K_2CO_3, extracted three times with 300 ml of ether, the organic phase dried over Na_2SO_4 and evaporated. Crystallization from ether gave 215.4 g (87 %) of 5, mp 119-121°.

IR (KBr): 3490, 3396, 1713, 1252; NMR: δ 1.40 (t, J = 7 Hz, 3H), 3.96 (s, 3H), 4.40 (q, J = 7 Hz, 2H), 7.08 (d, J = 2 Hz, 1H), 7.20 (d, J = 2 Hz, 1H); MS: 229 (100, M, Cl).

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.30 H, 5.27 N, 6.10 %
Found: C, 52.34 H, 5.31 N, 5.98 %

b) Catalytic Reduction with Pd-C.- A suspension of 279 g (1.08 mol) of 4 in 5 l of EtOH and 130 ml of conc HCl was hydrogenated at atmospheric pressure in the presence of 27.9 g of Pd-C (5 %). The reaction mixture was kept at room temperature by external cooling. During the reaction the starting material dissolved slowly. When the H_2-uptake was complete, the catalyst was filtered and the filtrate concentrated until crystallization started. The

hydrochloride of 5 (256 g, mp 196-200°) was obtained in two fractions. It was suspended in 1.5 l of water and after addition of an excess of 2N NaOH the mixture extracted with three portions of 800 ml of CH_2Cl_2. The organic layer was washed with 500 ml of H_2O, dried over $MgSO_4$ and the solvent evaporated. Trituration of the residue with ether gave 230 g (92 %) of 5, mp 120-124°.

Ethyl 4-chloro-3-formamido-5-methoxybenzoate (6).- A mixture of 4.6 g (0.02 mol) of 5 and 10.8 g of a 1:1 mixture of phenol and phenyl formate (0.044 mol) was heated overnight at 80°.After cooling and addition of ether, 4.1 g of pure 6 were collected, mp 151-152°. The mother liquors (10 g) were filtered through silica gel to give another 0.2 g of 6, mp 151-152°. The total yield was 4.3 g (84 %).

IR (KBr): 3376, 3290, 1715, 1694; NMR: δ 1.44 (t, J = 7 Hz, 3H), 4.01 (s, 3H), 4.46 (q, J = 7 Hz, 2H), 7.51 (d, J = 2 Hz, 1H), 7.5-9 (broad signal, 3H); MS: 257 (17, M, Cl).

Anal. Calcd. for $C_{11}H_{12}ClNO_4$: C, 51.27 H, 4.69 N, 5.44 Cl, 13.76 %
Found: C, 51.24 H, 4.67 N, 5.36 Cl, 13.89 %

Ethyl 4-chloro-3-methoxy-5-(methylamino)benzoate (7).- A mixture of 100 g (0.43 mol) of 5 and 37 g (0.43 mol) of formalin (35 %) in 300 ml of CH_3OH was hydrogenated in an autoclave for 16 hrs. at 90° at an initial pressure of 100 bar in the presence of 20 g of Raney nickel. The catalyst was filtered and the filtrate concentrated until crystallization started. In two fractions 78 g (74 %) of 7 were obtained, mp 64-69°.

4-Chloro-3-methoxy-5-(methylamino)benzyl alcohol hydrochloride (8)

a) From 6.- To a stirred suspension of 8 g (0.21 mol) of $LiAlH_4$ in 80 ml of THF under an argon atmosphere a solution of 13.6 g (0.053 mol) of 6 in 272 ml of THF was added over a period of 30 min. After the addition was complete, 3N NaOH was added dropwise until the gas evolution ceased. The solid was filtered and washed several times with ethyl acetate. The filtrate was evaporated to give 11.9 g of crude product which was treated with a saturated solution of hydrochloric acid in methanol. Addition of ether gave 10.3 g (82 %) of 8·HCl, mp 195-197°.

IR ($CHCl_3$): 3618, 3456; NMR (free base): δ 1.70 (broad signal, 1H), 2.92 (s, 3H), 3.90 (s, 3H), 4.55 (broad signal, 1H), 4.65 (s, 2H), 6.39 (s, 2H); MS: 201 (100, M, Cl).

Anal. Calcd. for $C_9H_{12}ClNO_2 \cdot HCl$: C, 45.40 H, 5.50 N, 5.88 %
Found: C, 45.29 H, 5.52 N, 5.80 %

b) From 7.- A solution of 32 g (0.13 mol) of 7 in 150 ml of dry THF was dropped slowly at room temperature to a stirred mixture of 400 ml of dry THF and 140.8 g (0.49 mol) of 70 % $NaAlH_2(OCH_2CH_2OCH_3)_2$ in toluene. Stirring was continued for 1 hr. The reaction mixture was cooled to 0° and 2N NaOH was added until gas evolution ceased. The mixture was filtered through Celite and the filtrate evaporated under reduced pressure. The residue was dissolved in 300 ml of ether and the solution acidified with ethanolic HCl to yield 16 g (51 %) of 8·HCl as white crystals, mp 190-191°.

4-Chloro-3-methoxy-5-(methylamino)benzaldehyde (9).- To 143 g (0.60 mol) of 8·HCl was added 500 ml of cold 2N NaOH and the mixture extracted three times with 200 ml of CH_2Cl_2. The organic layers were washed with brine and

dried over Na_2SO_4 to give after evaporation of the solvent 116 g of 8 as a brown oil. To a solution of this oil in 200 ml of pyridine was added under stirring within 1 hr. at 6° (ice bath) a solution of 120 g (1.2 mol) of CrO_3 in 120 ml of H_2O and 1.2 l of pyridine (prepared by slow addition of the aqueous solution of CrO_3 to pyridine under ice cooling). The reaction mixture was stirred 4 hrs. in the ice bath and 16 hrs. at ambient temperature. Then 0.5 l of ethyl acetate and 1 l of H_2O were added and the solution decanted from an insoluble residue which was further extracted with 1 l of warm ethyl acetate and 1 l of H_2O. The combined extracts were filtered through Celite to remove insoluble material and the aqueous phase was extracted with 1,5 l of ethyl acetate. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and freed from the solvent in vacuo. Chromatography of the residue (120 g) on silica gel (800 g; CH_2Cl_2) and crystallization of the eluated product from ether/hexane afforded 81.8 g of aldehyde 9 of mp 60-61°. Another 4.3 g, mp 61-62°, were obtained from the rechromatographed material of the mother liquor. The total yield was 86.1 g (72 %). An analytical sample, mp 58-59°, was obtained in a previous experiment.

IR ($CHCl_3$): 3450, 1699; NMR: δ 2.96 (d, J = 5 Hz, 3H), 3.94 (s, 3H), 4.52 (broad NH-signal, 1H), 6.81 (d, J = 2 Hz, 1H), 6.85 (d, J = 2 Hz, 1H), 9.95 (s, 1H); MS: 199 (100, M, Cl).

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.15 H, 5.05 N, 7.02 Cl, 17.76 %
Found: C, 54.28 H, 5.25 N, 6.93 Cl, 17.90 %

4-Chloro-3-methoxy-α-methyl-5-(methylamino)cinnamaldehyde (10).- To a stirred solution of 140 g (0.7 mol) of 9 and 14 g (0.25 mol) of KOH in 560 ml of ethanol was added within 1 hr. at a temperature of 15-16° a solution of 52.7 g (0.91 mol) of propionaldehyde in 140 ml of ethanol. Stirring

was continued for 1 hr. at 0° and then for 30 min. at -30°. The precipitated crystals were isolated by filtration and recrystallized from ethanol to give 103 g of yellow crystals, mp 97-98°. The mother liquor of the first crystallization was neutralized with acetic acid, the solvent removed and the remaining material filtered through silica gel to yield a mixture (25 g) of starting material and product. Together with the content of the second mother liquor this material was treated again with propionaldehyde and KOH in the described manner to furnish another 14.3 g of pure product, mp 96-98°. Yield 117.3 g (70 %). An analytical sample of mp 98-100° was recrystallized twice from ethanol.

IR (KBr): 3390, 1670 with shoulder 1685, 1622, 1600; NMR: δ 2.10 (d, J = 1 Hz, 3H), 2.95 (d, J = 5 Hz, 3H), 3.90 (s, 3H), 4.53 (broad N-H signal, 1H), 6.48 (broad s, 2H), 7.20 (broad s, 1H), 9.57 (s, 1H); UV: 267 (19950), 310 (17280) with shoulder 366 (3160); MS: 239 (100, M, Cl), 211 (98, M-CO, Cl).

Anal. Calcd. for $C_{12}H_{14}ClNO_2$: C, 60.13 H, 5.89 N, 5.84 Cl, 14.79 %
Found: C, 60.08 H, 5.95 N, 5.80 Cl, 15.07 %

α-[4-Chloro-3-methoxy-α-methyl-5-(methylamino)styryl]-1,3-dioxolane-2-propanol (11).- To a Grignard solution prepared from 116.2 g (0.66 mol) of 2-(2-bromoethyl)-dioxolane and 16.0 g (0.66 mol) of magnesium in 500 ml of dry THF according to the known procedure,[7] a solution of 59.0 g (0.246 mol) of 10 in 250 ml of dry THF was added dropwise at room temperature within 30 min. After stirring for 3.5 hrs. at 35°, the reaction mixture was poured into 850 ml of cold 15 % aq. NH_4Cl solution and extracted three times with 350 ml of ether. The combined organic layers were washed with H_2O, dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue crystallized from ether to afford 72.3 g of 11, mp 110-111°. The material

of the mother liquor was chromatographed on silica gel (200 g; CH_2Cl_2 containing 1 % of CH_3OH) to give after crystallization from ether another 5.1 g, mp 108-110° and 1.9 g, mp 107-108°. The yield was 79.3 g (94 %). An analytical sample of mp 110-111° was crystallized twice form ether.
IR (KBr): 3418, 1662, 1590, 1580; NMR: δ 1.88 (s, 3H) superimposed with 1.60-2.10 (m, 4H), 2.55 (broad OH-signal, 1H), 2.87 (d, J = 4 Hz, 3H), 3.83 (s, 3H) superimposed with 3.75-4.08 (m, 4H), 4.08-4.70 (broad signal with maximum at 4.13 and 4.33, 2H), 4.88 (m, 1H), 6.23 (s, 2H), 6.35 (s, 1H); MS: 341 (41, M, Cl), 73 (100).

Anal. Calcd. for $C_{17}H_{24}ClNO_4$: C, 59.73 H, 7.08 N, 4.10 Cl, 10.37 %
Found: C, 59.70 H, 7.04 N, 3.86 Cl, 10.48 %

2-Chloro-5-[5-(1,3-dioxolan-2-yl)-2-methyl-1,3-pentadienyl]-3-methoxy-N-methylaniline (12).- A solution of 10.2 g (0,03 mol) of 11 and 180 mg of p-toluenesulfonic acid in 240 ml of toluene and 3 ml of ethyleneglycol was heated at reflux for 4 hrs., the water being removed from the reaction mixture by means of a Dean-Stark trap. The cooled reaction mixture was concentrated in vacuo and the residue partitioned between sat. aq. $NaHCO_3$ and CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The residue was chromatographed on silica gel (210 g; CH_2Cl_2) and the collected product (5.4 g) crystallized from diisopropylether to afford 4.0 g (41 %) of 12, mp 79-81 %.
IR ($CHCl_3$): 3465, 1595 with shoulder 1615; NMR: δ 2.00 (d, J = 1 Hz, 3H), 2.53 (d x d, J = 5 and 7 Hz, 2H), 2.87 (d, J = 5 Hz, 3H), 3.85 (s, 3H) superimposed with 3.70-4.10 (m, 4H), 4.35 (broad NH-signal, 1H), 4.93 (t, J = 5 Hz, 1H), 5.75 (d x t, J = 16 and 7 Hz, 1H), 6.24 (s, 2H), 6.36 (d, J = 16 Hz, 1H),

6.42 (broad s, 1H); UV: 218 (19000), 250 (25650), 287 (25330) with shoulder 333 (3360); MS: 323 (10, M, Cl), 235 (12, Cl), 73 (100).

Anal. Calcd. for $C_{17}H_{22}ClNO_3$: C, 63.06 H, 6.85 N, 4.32 Cl, 10.95 %
Found: C, 62.91 H, 6.89 N, 4.21 Cl, 11.13 %

2,2,2-Trichloroethyl 2-chloro-5-(5-formyl-2-methyl-2,4-pentadienyl)-3-methoxy-N-methylcarbanilate (14 and 15).- 1.27 g (6.0 mmol) of β,β,β-trichlorethoxycarbonylchloride was added slowly to a solution of 1.62 g (5.0 mmol) of 12 in 20 ml of pyridine. A fine precipitate was formed immediately The reaction mixture was stirred at room temperature for 42 hrs., then poured into a mixture of 80 ml of 3N HCl and 30 g of ice and extracted three times with CH_2Cl_2. The combined organic layers were washed with 3N HCl, sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent evaporated in vacuo. To the remaining oil (2.75 g, 13), dissolved in 32 ml of acetone, was added 8 ml of 1N HCl and the solution heated at 50° for 5 hrs. under argon. The cooled reaction mixture was concentrated in vacuo and extracted three times with 40 ml of CH_2Cl_2. The organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent evaporated in vacuo. The crude product was chromatographed on silica gel (ethyl acetate/CH_2Cl_2/hexane 1:1:3). The pure fractions were evaporated, the remaining oil filtered with CH_2Cl_2 through 8 g of silica gel and the CH_2Cl_2 evaporated in vacuo. The residue was dried to afford 1.53 g (67 %) of a mixture of the dienals 14 and 15 as a pale yellow amorphous material. Based on the nmr spectrum, the ratio of 14:15 is about 2:1.

Anal. Calcd. for $C_{18}H_{19}Cl_4NO_4$: C, 47.50 H, 4.21 N, 3.08 Cl, 31.16 %
+ 0.08 mol CH_2Cl_2 Calcd.: C, 47.01 H, 4.18 N, 3.03 Cl, 31.93 %
Found : C, 46.75 H, 4.17 N, 3.08 Cl, 31.82 %

This procedure could be scaled up to 50 g (yields 60-70 %). The isomeric dienals 14 and 15 could be separated by chromatography on silica gel (ethyl acetate/hexane 1:3). Using two MERCK silica gel 60 packed columns (size C) in series (approximately 440 g of silica gel, 120-230 mesh), the chromatography of 2 g of crude isomeric mixture 14 and 15 afforded 502 mg of 15 and 805 mg of 14 of a geometrical purity $\geq$ 95 % each (based on NMR). A fraction of 224 mg of unseparated material could be recycled.

Dienal 14: Rf: 0.10 (SiO_2; ethyl acetate/hexane 1:3); IR ($CHCl_3$): 1726, 1679, 1630; UV: 287 (18200); NMR: δ 1.88 (s, 3H, vinylic CH_3), 3.26 (s, 3H, N-CH_3), 3.46 (s, 2H, benzylic CH_2), 3.90 (s, 3H, OCH_3), 4.46 and 4.91 (2 d, J = 12 Hz, 2H, CH_2CCl_3), 6.14 (d x d, J = 15 and 8 Hz, 1H, vinylic H), 6.20 (d, J = 11 Hz, 1H, vinylic H), 6.70 (d, J = 2 Hz, 1H, arom. H), 6.76 (d, J = 2 Hz, 1H, arom. H), 7.39 (d x d, J = 15 and 11 Hz, 1H, vinylic H), 9.60 (d, J = 8 Hz, 1H, -CHO), a minor rotamer exhibits distinct extra signals at 1.91 (s), 3.32 (s); ^{13}C NMR: δ 193.6 (d), 156.0 (s), 153.4 (s), 149.8 (s), 147.7 (d), 140.5 (s), 138.2 (s), 131.1 (d), 125.5 (d), 121.8 (d), 119.6 (s), 112.2 (d), 95.4 (s), 75.2 (t), 56.5 (q), 46.3 (t), 37.0 (q), 17.4 (q); MS: 453 (1, M, 4Cl), 418 (25, M-Cl, 3Cl), 95 (100). Dienal 15: Rf: 0.11 (SiO_2; ethyl acetate/hexane 1:3); IR ($CHCl_3$): 1726, 1680, 1636; UV: 287 (18500); NMR: δ 1.84 (s, 3H), 3.25 (s, 3H), 3.63 (s, 2H), 3.90 (s, 3H), 4.46 and 4.93 (2d, J = 12 Hz, 2H), 6.21 (d x d, J = 15 and 11 Hz, 1H), 6.35 (d, J = 11.5 Hz, 1H), 6.69 (d, J = 2 Hz, 1H), 6.73 (d, J = 2 Hz, 1H), 7.49 (d x d, J = 15 and 11.5 Hz, 1H), 9.63 (d, J = 8 Hz, 1H), a minor rotamer exhibits distinct extra signals at 1.88 (s), 3.31 (s); ^{13}C NMR: 193.6 (d), 156.0 (s), 153.5 (s), 149.1 (s), 146.9 (d), 140.7 (s), 138.2 (s), 131.3 (d), 126.2 (d), 121.4 (d), 119.7 (s), 111.7 (d), 95.4 (s), 75.2 (t), 56.5 (q), 38.4 (t), 37.0 (q), 24.7 (q); MS: 453 (1, M, 4Cl), 418 (10, M-Cl, 3Cl), 95 (100).

Equilibration of the Isomers 14 and 15

a) To 75 mg of E,Z-dienal 15[8] in 3 ml of acetone was added 0.8 ml of 1N HCl and the homogenous solution heated under argon at 50° for 2 hrs. The cooled reaction mixture was concentrated and partitioned between H_2O and CH_2Cl_2. The organic layer was washed with aq. $NaHCO_3$ and brine and dried over Na_2SO_4. After evaporation of the solvent, 71 mg of a pale yellow oil remained which in the nmr spectrum proved to be a 2:1 mixture of the E,E- and E,Z-isomers 14 and 15.

b) Under the same reaction conditions a sample of E,E-dienal 14[8] could be equilibrated to yield a 2:1 mixture of 14 and 15.

2-Chloro-5-[(E,E)-6-(1,3-dithian-2-yl)-6-methoxy-2-methyl-2,4-hexadienyl]-3-methoxy-N-methylaniline (16) and α-[(E,E)-5-[4-Chloro-3-methoxy-5-(methylamino)phenyl]-4-methyl-1,3-pentadienyl]-1,3-dithiane-2-methanol (17)

a) To a solution of 361 mg (3 mmol) of 1,3-dithiane in 10 ml of dry THF was added dropwise at -50° 1.31 ml of 2.4 M BuLi in hexane. The solution was kept at -20° for 2.5 hrs., then cooled to -60° and added dropwise by means of a syringe to a solution of 1.307 g (2.87 mmol) of E,E-dienal 14 in 6 ml of dry THF at -78°. After stirring for 15 min., the solution was allowed to warm up to -40° over a period of 15 min., whereupon a solution of 4.56 g (32 mmol) of CH_3I in 7 ml of HMPT was added. The dark solution was stored at -15° for 4 hrs. and then poured into 50 ml of ice-cold 15 % aq. NH_4Cl solution and the mixture extracted with 150 ml of ether. The organic layers were washed with aq. NH_4Cl and brine, dried over Na_2SO_4 and the solvent evaporated. The remaining oil (2.1 g) was filtered through silica gel (8 g; ethyl acetate/hexane 1:1) to remove polar impurities and the solution of the crude product (1.85 g) in 40 ml of CH_3OH and 0.8 ml of acetic acid refluxed for 4 hrs. under argon in the presence of 8 g of Zn powder (freshly

activated by 3N HCl and washed with H_2O and ethanol). Insoluble material was filtered and the filtrate concentrated and partitioned between 100 ml of CH_2Cl_2 and 40 ml of 5 % acetic acid. The organic layers were washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and the solvent evaporated. The remaining oil (1.14 g) was chromatographed on 80 g silica gel (ethyl acetate/CH_2Cl_2/hexane 1:1:3) to yield 419 mg (35 %) of the dithiane 16.

Rf: 0.37 (SiO_2; ethyl acetate/hexane 1:2); NMR: δ 1.75 (s, 3H, vinylic CH_3), 1.80-2.23 (m, 2H, CH_2-$\underline{CH_2}$-CH_2), 2.88 (s, 3H, N-CH_3) superimposed with 2.70-3.07 (m, 4H, S$\underline{CH_2}CH_2\underline{CH_2}$S), 3.30 (s, 2H, benzylic CH_2), 3.35 (s, 3H, OCH_3), 3.85 (s, 3H, arom. OCH_3) superimposed with 3.67-3.98 (m, 1H, $\underline{CH}$-OCH_3), 4.26 (d, J = 5.5 Hz, 1H, SCHS), 4.37 (broad NH-signal, 1H), 5.59 (d x d, J = 15 and 8 Hz, 1H, vinylic H), 5.96 (d, J = 11 Hz, 1H, vinylic H), 6.14 (s, 2H, arom. H), 6.53 (d x d, J = 11 and 15 Hz, 1H, vinylic H); MS: 413 (2.6, M, Cl), 381 (10, M-CH_3OH, Cl), 294 (49, Cl), 236 (62, Cl), 119 (100);

Elemental composition of M: Found 413.1230

Calcd. for $C_{20}H_{28}ClNO_2S_2$ 413.1249

In the nmr spectrum of 16 no signals of the E,Z-isomer (see b) could be detected, thus confirming the isomeric purity to be $\geq$ 90 %.

From a more polar fraction, 174 mg (15 %) of the alcohol 17 could be isolated.

Rf: 0.18 (SiO_2; ethyl acetate/hexane 1:2); NMR: δ 1.73 (s, 3H), 1.65-2.22 (m, 2H), 2.88 (s, 3H) superimposed with 2.42-3.12 (m, 4H), 3.30 (s, 2H), 3.87 (s, 3H), 3.98 (d, J = 7 Hz, 1H), 4.15-4.65 (m, 2H), 5.73 (d x d, J = 15 and 7 Hz, 1H), 5.97 (d, J = 11 Hz, 1H), 6.18 (s, 2H), 6.67 (d x d, J = 15 and 11 Hz); MS: 399 (1.7, M, Cl), 381 (100, M-H_2O, Cl);

Elemental composition of M: Found 399.1066

Calcd. for $C_{19}H_{26}ClNO_2S_2$ 399.1093

b) In a preliminary experiment a 2:1 mixture of the dienals 14 and 15 was reacted with 2-lithio-1,3-dithiane in the above described manner. After in situ methylation a 2:1 mixture of 16 and the corresponding E,Z-isomer was isolated chromatographically (SiO_2; ethyl acetate/CH_2Cl_2/hexane 1:1:3) in 40 % yield.

Rf: 0.37 (SiO_2; ethyl acetate/hexane 1:2); NMR signals of the E,Z-isomer: only the olefinic protons were clearly distinguishable in the mixture, i.e. δ 5.63 (d x d, J = 15 and 10 Hz, 1H), 6.09 (d, J = 11 Hz, 1H), 6.64 (d x d, J = 15 and 11 Hz, 1H).

2-Chloro-3-methoxy-N-methyl-5-(2-nitro-1-propenyl)aniline (18).- A solution of 20 g (0.1 mol) of 9 and 9.6 g (0.125 mol) of ammonium acetate in 200 ml of nitroethane was refluxed for 15 min. The reaction mixture was cooled and 200 ml of CH_2Cl_2 was added and the solution cooled with dry ice. The precipitate was filtered, washed with 200 ml of ice-cold CH_2Cl_2 and the filtrate was evaporated. Crystallization from ether yielded 22 g (86 %) of 18, mp. 84-85°.

IR (KBr): 3550, 3426, 1649; NMR: δ 2.46 (d, J = 1 Hz, 3H), 2.92 (d, J = 5 Hz, 3H), 3.90 (s, 3 Hz), 4.5 (broad signal, 1H), 6.34 (d, J = 2 Hz, 1H), 6.37 (d, J = 2 Hz, 1H), 8.0 (broad s, 1H); MS: 252 (100, M, Cl).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47 H, 5.10 N, 10.91 Cl, 13.81 %

Found: C, 51.58 H, 5.08 N, 10.80 Cl, 13.74 %

1-[4-Chloro-3-methoxy-5-(methylamino)phenyl]-2-propanone (19).- To a solution of 11.3 g (0.044 mol) of 18 in 113 ml of ethanol was added 282 ml of H_2O and the reaction heated to 80° with stirring. Then 16.9 g of Fe powder and 0.66 g of $FeCl_3$ was added in one portion, followed by dropwise addition of 11 ml of conc. HCl. After the addition was complete, the reaction was left at reflux temperature for 4 hrs. The solid residue was filtered and washed with 200 ml of methanol, then with 200 ml of hot water. The filtrate was evaporated under vacuum and 1 l of water was added to the residue. The pH was made basic by portionwise addition of Na_2CO_3. The aqueous phase was extracted three times with 50 ml of ether, the organic layer was dried, evaporated and the crude product chromatographed on silica gel (benzene/ether 9:1) to yield 8.55 g (86 %) of pure liquid 19.
Rf: 0.40 (SiO_2; benzene/ether 9:1); IR (neat): 3426, 1711; NMR: δ 2.17 (s, 3H), 2.39 (s, 3H), 3.60 (s, 2H), 3.86 (s, 3H), 4.40 (broad signal, 1H), 6.16 (s, 2H); MS: 227 (90, M, Cl).

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8. Geometrical purity based on nmr $\geq$ 95 %.

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