but in these cases attack at nitrogen may also lead to the ortho sulfate as well as to the other oxidation products previously discussed.[2]

Sabesan and Venkatasubramanian[4] have measured the rate constant for the reaction between *N,N*-dimethylaniline and peroxodisulfate ion under substantially the same conditions as those given in Table I. We confirm their value (1.7 M^{-1} min^{-1}) and point out that the rates we observe for the *o*-methyl derivatives are all of the order of one-tenth of this value. Diminished reactivity for the reactions of ortho-substituted *N,N*-dialkylanilines with electrophiles to yield ortho- and para-substituted anilines is well-known[12] and has been shown to be due to steric inhibition of resonance forms such as **5**. This effect also reflects itself in the increased basicity of the ortho-substituted *N,N*-dialkylanilines.[13] Therefore, were peroxodisulfate to attack at nitrogen, we would expect that the ortho-substituted *N,N*-dimethylanilines would react more rapidly than the parent *N,N*-dimethylanilines. The opposite is the case. Since the substituent effect discussed above argues against rate-limiting attack at the available ortho carbon, the decreased rate of reaction for the ortho-substituted *N,N*-dimethylanilines is also consistent with reaction at the ipso position.

Experimental Section

The primary anilines, supplied by Aldrich, were converted to *N,N*-dimethylanilines according to the procedure of Billman et al.[14] The IR spectra showed no NH stretch. Other physical properties of the *N,N*-dimethylanilines follow.

2,3-Dimethyl: bp 105–105.5 °C (28 mm); n^{25}_D 1.5245 (lit.[13] 1.5241); NMR δ 2.18 (s, 6, Me, Me), 2.58 (s, 6, NMe_2), 6.86 (m, 3).

2,4-Dimethyl: bp 100–101.5 °C (27 mm); n^{25}_D 1.5165 (lit.[13] 1.5170); NMR δ 2.22 (s, 3, Me), 2.25 (s, 3, Me), 2.58 (s, 6, NMe_2), 6.85 (s, br, 3).

2-Methyl-3-chloro: bp 120.5–122 °C (28 mm); n^{25}_D 1.5440; NMR δ 2.34 (s, 3, Me), 2.60 (s, 6, NMe_2), 6.9 (m, 3).

2-Methyl-4-chloro: bp 121–122 °C (26 mm); n^{25}_D 1.5410; NMR δ 2.25 (s, 3, Me), 2.60 (s, 6, NMe_2), 6.9 (m, 3).

The NMR data were taken at 35 °C at 60 MHz in CCl_4 with Me_4Si as internal standard. Kinetics were carried out under pseudo-first-order conditions, peroxodisulfate limiting, as previously described.[2] Product from 2,3-dimethyl-*N,N*-dimethylaniline was detected in the ethanol-soluble fraction of reaction mixtures upon paper electrophoresis at pH 8 as a UV-absorbing, negatively charged species with a mobility slightly less than that of picrate ion. This material reduced the Folin phenol reagent but not the Folin–Denis uric acid reagent.[15] Following hydrolysis in acid, the product reduced the uric acid reagent as well. Quantitative estimation with the uric acid reagent[15] suggested a yield in the 30–40% range in accord with previous work.[2]

Registry No.—Peroxodisulfate, 15092-81-6.

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Structure, Absolute Configuration, and Synthesis of Stramonin-B, a New Cytotoxic Pseudoguaianolide

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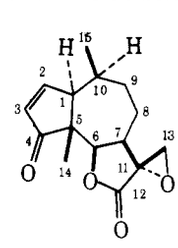
In our continuing investigation of naturally occurring and synthetic sesquiterpene lactones that exhibit antitumor and allergenic properties,[1] a new sesquiterpene lactone has been isolated from the chloroform extracts of the medicinal plant *Parthenium tomentosum* var. *stramonium* (Compositae).[2] We report the isolation, structural elucidation, absolute configuration, and synthesis of stramonin-B (1), the first naturally occurring epoxidized α-methylene lactone of a pseudoguaianolide. Stramonin-B exhibited significant activity



1

(ED_{50} = 2.9 μg/mL) in vitro against KB cells in tissue culture.[3,4]

Chromatography on activated silica gel of a chloroform extract of ground leaves of *Parthenium tomentosum* var. *stramonium* (Greene) Rollins resulted in isolation (0.07%) of a new pseudoguaianolide. Stramonin-B (1), crystallized from isopropyl ether–chloroform: mp 175–176 °C; $[\alpha]^{27}_D$ −125° (*c* 1.14, chloroform).

The ^1H NMR spectrum (250 MHz, $CDCl_3$) of stramonin-B [$C_{15}H_{18}O_4$, M^+ *m/e* 262, UV (MeOH) 226 nm (ε 8947)] exhibited a one-proton doublet of doublets (*J* = 2 Hz, 6 Hz) located at δ 7.48 and a one-proton doublet of doublets (*J* = 3 Hz, 6 Hz) at δ 6.12 which, together with IR (KBr) bands at 1720 and 1595 cm^{-1}, indicated the presence of a cyclopentenone ring. The IR spectrum also showed a band at 1775 cm^{-1} (γ-lactone) and a series of bands at 1250, 980, and 835 cm^{-1} (terminal epoxide). The nature of the epoxide (terminal disubstituted) was elucidated from the ^1H NMR spectrum which revealed a two-proton AB quartet (*J* = 5.5 Hz) centered at δ 3.29 ($\Delta\nu_{AB}$ = 36.1 Hz). The ^1H NMR spectrum also indi-

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cated the presence of a three-proton singlet at δ 1.24 (C-5 methyl) and a three-proton doublet at δ 1.05 (J = 7 Hz (C-10 methyl)). The richly detailed ^{1}H NMR spectrum of stramonin-B suggested that the C-10 proton at δ 2.24 is coupled to the protons of the methyl group at C-10 (confirmed by decoupling). Further decoupling experiments established the position of the epoxide moiety at C-11, C-13. The doublet (J = 9 Hz) at 4.78 was assigned to the C-6 proton thus establishing the position of the γ-lactone. Having established the presence of a pseudoguaianolide ring system, we resorted to single-crystal X-ray diffraction analysis in order to determine unambiguously the detailed structure and stereochemistry of stramonin-B. X-ray analysis of stramonin-B established unequivocally the relative stereochemistry depicted in Figure 1.

Stramonin-B crystallized in space group $P2_12_12_1$ with unit cell constants a = 8.449 (1), b = 23.822 (2), c = 6.465 (1) Å, V = 1301.2 Å^3, and Z = 4. Integrated intensities of 1578 independent reflections with $\theta \leq 75°$ were measured on an Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation. Of these reflections, 1388 were considered as observed ($I \geq 2\alpha_1$). The structure was determined using the direct method program QTAN[5] and refined by full-matrix least squares. The positions of the 18 hydrogen atoms were determined by difference Fourier techniques. The hydrogen atomic coordinates and isotropic thermal parameters were included, but not refined, in the final cycles of least-squares refinement. The conventional R indices are 4.9% for the 1388 observed data and 7.1% for all data. Figure 1 shows a stereoview of the conformation of stramonin B. The *relative* configuration of the asymmetric carbons C-1, C-5, C-6, C-7, C-10, and C-11, as shown in structure **1**, can be specified as C-1(S), C-5(R), C-6(R), C-7(R), C-10(S), C-11(R). Because of the weak anomalous dispersion of oxygen ($\Delta f''$ = 0.032 e for Cu Kα) no attempt was made to determine the absolute configuration of stramonin-B (vide infra).

Even though hydrogen positions could be clearly discerned about C-13, leading us to assign the relative stereochemistry of the epoxide ring as indicated in Figure 1, three additional full-matrix least-squares refinement cycles were done after convergence at R_{obsd} = 4.9%, because of our particular interest in the configuration at C-11. In these refinement cycles the C-13 and oxygen positions were interchanged. The residual increased to a R_{obsd} value of 9.3%, confirming the correctness of the model with the relative α-oriented oxygen and β-oriented carbon configuration shown in Figure 1.

The cyclopentenone ring has a C-5 envelope conformation with an average torsion angle equal to 13.9°. A pseudo-mirror plane passes through atom C-5 and the midpoint of the C-2–C-3 bond and the asymmetry parameter[6] ΔC_s is 0.9°. The γ-lactone ring has a C-12 half-chair conformation with an average torsion angle of 16.1°. A pseudo-twofold axis passes through atom C-12 and the midpoint of the C-6–C-7 bond with an asymmetry parameter ΔC_s of 1.4°. The seven-membered ring is a deformed half-chair. An asymmetry parameter ΔC_2 of 2.2° is calculated for the pseudo-twofold axis passing through atom C-10 and the midpoint of the C-6–C-7 bond. The average torsion angle of the ring is equal to 57.9°. The junctions C-1–C-5 and C-6–C-7 are respectively trans and cis.

The absolute configuration of stramonin-B was deduced by transformation of (−)-damsin (**2**) into (−)-stramonin-B (**1**). The conversion of damsin into **1** constitutes a formal total synthesis of stramonin-B.[7] (−)-Damsin of established absolute configuration[8] was treated with osmium tetroxide in anhydrous tetrahydrofuran containing dry pyridine. The resulting osmate ester upon treatment with hydrogen sulfide[9] provided an 81% yield of crystalline diol **3**, mp 168–169 °C. As anticipated the isomeric diol which would have resulted from β attack on the carbon–carbon double bond could not be detected. Diol **3** was converted into monomesylate **4** which was dissolved in benzene and treated with 1,5-diazabicyclo[5.4.0]undec-5-ene. Purification of the crude reaction mixture on silicAR CC-7 gave a 78% overall yield of pure crystalline epoxide **5**, mp 137–138 °C. Epoxide **5** was identical in all respects (NMR, IR, $[\alpha]_D$ TLC, mmp) with a sample derived from natural stramonin-B by reduction of the cyclopentenone double bond.

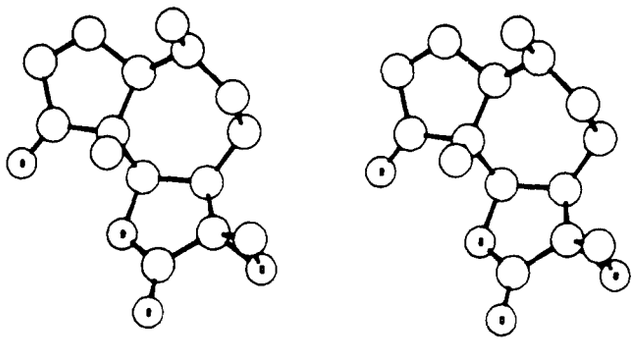
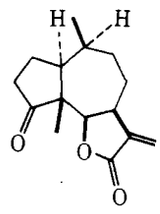


Figure 1. A stereoview of stramonin-B (**1**). No hydrogen atoms are shown. Oxygen atoms are denoted by small dots at their centers. The orientation is arbitrary.



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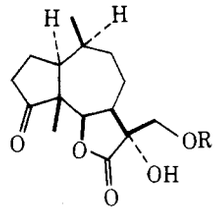
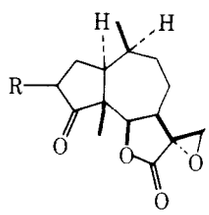


3, R = H
4, R = SO_2CH_3

Selenenylation[10] of epoxy ketone **5** in ethyl acetate employing phenyl selenenyl chloride in the presence of Dowex 50-X8 (H^+) gave selenide **6** in 77% yield. Oxidation of **6** with sodium periodate in tetrahydrofuran–water (6:1) provided a 60% yield of pure crystalline (−)-stramonin-B, mp 175–176 °C, identical in all respects with the sample from natural sources.



5, R = H
6, R = SeC_6H_5

Experimental Section

Melting points were determined on a Fisher-Johns hot-stage melting-point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrophotometer and nuclear magnetic resonance (NMR) spectra were recorded at 250 MHz. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} = 0.0 ppm) as an internal standard. The ^{13}C spectra were obtained on a Jeolco FX-60. UV spectra were recorded on a Varian Super Scan 3 spectrophotometer. High-resolution mass spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were prepared by Galbraith Laboratories, Inc., Knoxville, Tenn.

Isolation of Stramonin-B. A collection of *Parthenium tomentosum* var. *stramonium* (ER 147 collected in the vicinity of Quiriego, Sonora, Mexico on December 26, 1973) was extracted. The voucher

specimens of this collection are deposited in the University of Texas and the University of California, Irvine herbaria.

Dried leaf material (250 g) of *Parthenium tomentosum* var. *stramonium* was ground in a disk mill and extracted with chloroform at room temperature for 24 h using a mechanical stirring apparatus. Workup in the usual manner provided a thick residue which after precipitation with lead(II) acetate yielded 2.5 g (0.1%) of a yellow syrup. The syrup was chromatographed on a 5.2 × 43 cm column of activated silica gel. A solvent mixture of benzene and acetone (5:1) was used as the eluent and 25-mL fractions were collected.

All fractions were monitored on silica gel TLC plates (benzene–acetone 4:1 v/v) and fractions 15–35 were combined and evaporated to yield 105 mg of crude crystals of stramonin-B. Recrystallization of stramonin-B from isopropyl ether–chloroform gave pure crystals of **1**: mp 175–176 °C; $[\alpha]^{27}_D$ −125° (*c* 1.14, chloroform); IR (KBr) 3098, 2975, 2952, 2925, 2870, 1775, 1720, 1595, 1478, 1470, 1465, 1392, 1385, 1375, 1338, 1318, 1294, 1268, 1250, 1218, 1209, 1168, 1121, 1100, 1070, 1045, 1024, 1009, 980, 960, 926, 880, 870, 860, 835, 800, 765, 745, 730, 703 cm^{-1}; NMR (250 MHz) δ $CDCl_3$ 7.48 (dd, 1 H, $J_{2,3}$ = 6 Hz, $J_{1,2}$ = 2 Hz, 2-H), 6.12 (dd, 1 H, $J_{2,3}$ = 6 Hz, $J_{1,3}$ = 3 Hz, 3-H), 4.78 (d, 1 H, *J* = 9 Hz, 6-H), 3.29 (ABq, 2 H, *J* = 5.5 Hz, $\Delta\nu_{AB}$ = 36.1 Hz, 13-H), 3.20 (m, 1 H, 7-H), 3.00 (m, 1 H, 1-H), 2.42 (m, 1 H, 10-H), 2.0–1.5 (m, 4 H, 8-H, 9-H), 1.24 (s, 3 H, 14-H), 1.05 (d, 3 H, *J* = 7 Hz, 15-H); ^{13}C NMR ($CDCl_3$) δ 17.0 [C(14)],[11] 17.5 [C(15)],[11] 21.4 [C(9)],[11] 29.2 [C(8)],[11] 33.4 [C(10)], 3.99 [C(7)], 47.0 [C(1)], 51.6 [C(13)], 55.1 [C(5)],[11] 57.2 [C(11)],[11] 80.3 [C(6)], 131.4 [C(3)], 163.2 [C(2)], 173.5 (C(12)], 210.1 [C(4)]; UV (MeOH) 226 mm (ε 8947). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; M^+ 262.1205. Found: C, 68.55; H, 6.90; M^+ 262.1203.

Transformation of Damsin (2) into Dihydrostramonin-B (5). A solution of natural damsin (40 mg, 0.161 mmol) in 1.0 mL of anhydrous tetrahydrofuran was treated with osmium tetroxide (48 mg, 0.193 mmol) in pyridine (192 μL). After 20 min at room temperature, 10 mL of anhydrous ether was added to precipitate the osmate ester. The filtered osmate ester was dissolved in chloroform (10 mL) and treated with hydrogen sulfide gas until the chloroform solution was saturated. The resulting black solution was filtered through celite. Evaporation of the solvent gave the crude diol as a brown oil which was purified on silica gel. Elution with ethyl acetate gave 37 mg (80%) of pure **3** as colorless crystals: mp 168–169 °C: IR ($CHCl_3$) 3540, 1760, 1739 cm^{-1}; NMR (60 MHz) δ $CDCl_3$ 4.90 (d, 1 H, *J* = 6 Hz, 6-H), 4.05–3.48 (m, 4 H, CH_2OH, OH), 1.19 (s, 3 H), 1.10 (d, 3 H, *J* = 7 Hz).

Crystalline diol **3** (30 mg, 0.106 mmol) dissolved in 300 μL of methylene chloride was treated at room temperature with methanesulfonyl chloride (16 μL, 0.212 mmol) and pyridine (34 μL, 0.424 mmol). After 3.5 h, the reaction mixture was taken up in ethyl acetate (25 mL), washed with water (2 mL) and brine (1 mL), and dried over anhydrous magnesium sulfate. The crude mesylate **4** obtained after evaporation of the solvent in vacuo was dissolved in benzene (1.5 mL) and sittired for 1 h at room temperature in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (48 μL, 0.318 mmol). The reaction mixture was directly chromatographed on 5.0 g of silicAR CC-7. Elution with ether provided 22 mg (78%) of pure epoxide **5** as a colorless solid. Recrystallization using ethyl acetate–hexane gave analytically pure **5**, mp 137–138 °C, as colorless prisms: IR ($CHCl_3$) 3025, 2960, 2940, 2880, 1784, 1741, 1478, 1463, 1450, 1410, 1390, 1378, 1338, 1320, 1278, 1248, 1210, 1180, 1155, 1125, 1105, 1055, 1020, 1008, 983, 975, 940, 910, 890, 874 cm^{-1}; NMR (250 MHz) δ $CDCl_3$ 4.72 (d, 1 H, *J* = 9.1 Hz, 6-H), 3.18 (ABq, 2 H, *J* = 5.5 Hz, $\Delta\nu_{AB}$ = 21.1 Hz, 13-H), 3.01 (m, 1 H, 7-H), 1.14 (s, 3 H), 1.09 (d, *J* = 7 Hz); $[\alpha]^{25}_D$ −1.55° (*c* 1.35, $CHCl_3$), $[\alpha]_{436}$ +58.8 (*c* 1.35, $CHCl_3$). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.62. Found: C, 68.10; H, 7.74.

Dihydrostramonin-B (5). A mixture of 150 mg (0.572 mmol) of natural stramonin-B and 15 mg of 10% palladium on carbon in 45 mL of absolute ethanol was stirred in an atmosphere of hydrogen at room temperature for 1 h. Filtration of the catalyst through celite and evaporation of the solvent under reduced pressure gave crude **5** as a colorless oil which was chromatographed on 15 g of silicAR CC-7. Elution with ether gave 146 mg (97%) of pure dihydrostramonin-B, mp 137–138 °C (mmp 137–138 °C), as colorless crystals. This substance was identical in all respects with the sample of **5** prepared above from natural damsin.

Conversion of Dihydrostramonin-B into Stramonin-B. To a solution of dihydrostramonin-B (11.0 mg, 0. mmol) in ethyl acetate (400 μL) containing 4 mg of Dowex 50W × 8 (H^+ form) (washed with distilled water and ethyl acetate prior to use) was added phenyl selenenyl chloride (16.0 mg, 0.08 mmol). After 18 h at room temperature 4 mL of benzene was added and the solvent was removed in vacuo. The crude product was purified on 10.0 g of silicAR CC-7 using benzene–ether (5:1). The pure selenenylated ketone **6** (13 mg, 77% yield) was used directly in the next reaction.

A solution of ketone **6** (8.0 mg, 0.019 mmol) in 300 μL of tetrahydrofuran and 50 μL of water was stirred at room temperature for 3 h in the presence of sodium periodate (12.2 mg, 0.057 mmol). The reaction mixture was diluted with ethyl acetate (20 mL), washed with brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 5 mg of crude stramonin-B. Chromatography on 6.0 g of silicAR CC-7 (elution with ether) gave 3 mg (60%) of pure crystalline stramonin-B, mp 175–176 °C, identical in all respects (IR, NMR, $[\alpha]_D$, TLC, mmp) with the sample from natural sources.

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Registry No.—**1**, 65179-88-6; **2**, 1216-42-8; **3**, 67662-548; **4**, 67662-55-9; **5**, 67662-56-0; **6**, 67662-57-1; methanesulfonyl chloride, 124-63-0; phenylselenyl chloride, 5707-04-0.

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(3) Stramonin-B (**1**) demonstrated activities of 86–101% test/control (T/C) at dose levels ranging from 2.50–10.0 mg/kg in the PS test system.
(4) Antileukemic and in vitro cytotoxicity were assayed under the auspices of the National Cancer Institute by the procedure described in *Cancer Chemother. Rep.*, **25**, 1 (1962).
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