solid (95%). This was crystallized from hot carbon tetrachloride/petroleum ether to give white light fluffy needles, mp 195.0–196.5 °C dec.

Methyl (3-Methoxy-4,6-dimethyl-1-oxocyclohex-2-en-5-yl)acetate (19). (2,6-Dimethyl-3,5-dimethoxyphenyl)acetic acid (M_r = 224.2, 215 mg, 0.95 mmol) was dissolved in 20 mL of dry THF and 30 mL of dry *tert*-butyl alcohol and cooled under N_2 to −78 °C, at which time 100 mL of dry methylamine was distilled in. Li^0 (1.5 g, 216 mmol) was added all at once, and the reaction was warmed to −5 °C, no blue color being present until the reaction reached −15 °C. The temperature was maintained at −5 °C (ice/brine) for 20 min, when an additional 15 mL of *tert*-butyl alcohol was added. After about 5 min the blue color dissipated, and the flask was recooled to −78 °C, quenched with 30 g of NH_4Cl(s), and allowed to warm to room temperature overnight in a stream of nitrogen. The residual volatiles were aspirated off, the vacuum was broken with 40 mL of 1 M HCl, and the remaining mixture was extracted with ether. Workup produced 139 mg of pale oil (73%). This was immediately dissolved in 2 mL of MeOH and 2 mL of THF, and 15 mL (excess) of ethereal diazomethane was added. After 10 minutes, the volatiles were evaporated and the sweet-smelling resultant oil was distilled [Kugelrohr, 100 °C (0.01 mm Hg)] to give 107 mg (50%) of clear oil. The mixture of isomers (NMR 5.25 (1 h, br s), 3.62 (3 H, s), 3.60 (3 H, s), 2.9–2.1 (5 H, m), 1.25–1.00 (6 H, m)) was separated on silica TLC (ether/petroleum ether, 1:4, developed 7 times) to give the major kinetic product pure, which was assigned the all-cis configuration on the basis of 270-MHz decoupling experiments.

(3-Methoxy-4,6-dimethyl-1-oxocyclohex-2-en-5-yl)acetic Acid (18). (3,5-Dimethoxy-2,6-dimethylphenyl)acetic acid (M_r = 224, 790 mg, 3.52 mmol) was dissolved in 10 mL of dry THF and 10 mL of dry *tert*-butyl alcohol and cooled to −78 °C, and 100 mL of methylamine was distilled in. The reaction was warmed to −5 to −10 °C, and 0.5 g of Li^0 (M_r = 7, 70 mmol) was added piecemeal over 30 min. The blue solution was quenched with 5 mL of MeOH and recooled to −78 °C, 200 mmol of NH_4Cl was added, and the reaction was warmed to room temperature in an N_2 stream. The residual volatiles were aspirated off, the flask was cooled to 0 °C, and the vacuum was broken with 40 mL of saturated oxalic acid dihydrate in MeOH to pH 2. The solvent was evaporated, and the residuum was extracted with ether vs. pH 2 water. Workup produced 953 mg of pale oily semisolid, contaminated by a little oxalic acid. The product was distilled [120 °C (0.01 mmHg)] to give 544 mg of pale oil (73%). The isomer mixture could with difficulty be separated by TLC (50% C_6H_6, 50% ether, 1% HOAc, developed 4 times on 0.25-mm silica, or 80% C_6H_6, 20% ether, 1% HOAc, developed 10 times on 1-mm silica) to give two bands predominantly. The lower, and major, band was assigned the all-cis configuration (NMR, Table I). The higher, and lesser, band appeared to contain two isomers: NMR ($CDCl_3$) 5.34 (1 H, v br), 3.69 (3 H, br s), 3.0–2.0 (5 H, v br), 1.26 (3 H, br), 1.17 (3 H, br); NMR (Me_2SO-d_6, 125 °C) 5.26 (0.25 H, s), 5.21 (0.75 H, s), 3.66 (3 H, s), 2.6–1.9 (5 H, br), 1.25 (0.8 H, d, J = 6.8 Hz), 1.21 (0.8 H, d, J = 8.0 Hz), 1.09 (2.2 H, d, J = 6.7 Hz), 0.98 (2.2 H, d, J = 7.0 Hz).

Acknowledgment. We thank the National Cancer Institute for partial financial support of this research under Grant CA-24058. We also thank Dr. Brian McKittrick for performing the variable-temperature/decoupling NMR studies, Dr. Robert Serino and Dr. John Burke for the mass spectra, and Leo Slater for invaluable technical assistance.

Registry No. **1a**, 118-41-2; **1b**, 1916-07-0; **1c**, 96213-26-2; **1d**, 96213-27-3; **2a**, 1132-21-4; **2b**, 2150-37-0; **2c**, 96213-28-4; **3a**, 4670-10-4; **3b**, 6512-32-9; **3c**, 96213-29-5; **3d**, 96213-30-8; **4a**, 96213-31-9; **4b**, 96213-32-0; **5**, 96213-33-1; **6**, 96227-67-7; **6** methyl ester, 96213-34-2; **7**, 96213-35-3; **7** methyl ester, 96213-36-4; **8**, 96213-37-5; **8** methyl ester, 96213-38-6; **9**, 96213-39-7; **9a**, 75339-75-2; **10**, 96213-40-0; **11**, 96213-41-1; **12**, 96227-68-8; **13**, 96213-42-2; **14**, 96213-43-3; **15**, 96213-44-4; **16**, 96227-69-9; **17**, 96213-45-5; **18** (*all-cis*), 96213-46-6; **18**, 96290-75-4; **19** (*all-cis*), 96213-47-7; **19**, 96290-45-8; **20**, 96213-48-8; MTMCl, 2373-51-5; $ZnCl_2$, 7646-85-7; 3,4,5-trihydroxybenzoic acid methyl ester, 99-24-1; 1,3,5-trioxane, 110-88-3.

Synthesis of 2,2-Disubstituted 7-Methylenenorbornanes with 2-Exo Functionality by Diels–Alder Reaction of 5,5-Dimethoxytetrachlorocyclopentadiene[1]

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Received October 30, 1984

Diels–Alder reaction of 5,5-dimethoxytetrachlorocyclopentadiene (**2**) with methyl methacrylate gave only the *endo*-carbomethoxybicycloheptene adduct **4N**, confirmed by single-crystal X-ray analysis. Methylation of the endo adduct **3** of methyl acrylate and **2** gave only **4N**. Saponification and dehalogenation of **3** gave carboxy ketal **7**, whose methyl ester **9** also gave only *endo*-carbomethoxy product **10** upon alkylation. Reaction of **2** with methacrylonitrile gave a 3.5:1 exo/endo product mixture, whose major isomer **11X** was hydrolyzed to its carboxamide (**12X**). Conversion of **12X** to its carboxylic acid (**6X**) by acidic *n*-butyl nitrite was accompanied by a pentachloro byproduct (**19**) derived from internal methoxylation of the carboxy group by the C7 ketal. Dehalogenation of **6X** and hydrogenation gave saturated carboxy ketal **20**. Hydrolysis of **20** gave the lactol **22** of the keto acid. Treatment of **22** with diazomethane gave keto ester **25**; treatment of **20** with diazomethane gave ester **24**, whose ketal function could not be selectively hydrolyzed to give **25**, only **22** being isolated. Wittig reaction of **25** provided the 7-methylene ester **26**, also available by direct Wittig treatment of **22** followed by esterification.

For a study concerning haptophilic control of hydrogenation stereochemistry,[2] we undertook the synthesis of system **1**, in which the group R was to be modifiable to produce functions of differing size and polarity. Our ap-

(1) Taken in part from the Ph.D. Thesis of J. K. W., Rutgers University, 1984.

(2) Thompson, H. W.; Naipawer, R. E. *J. Am. Chem. Soc.* **1973**, *95*, 6379.

0022-3263/85/1950-2115$01.50/0

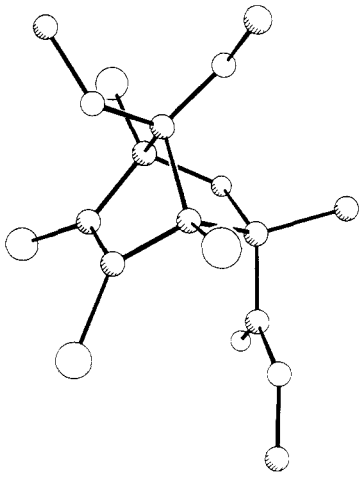
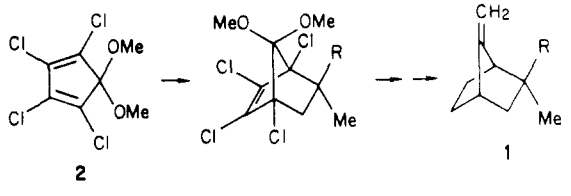


Figure 1. Compound **4N**.[8]

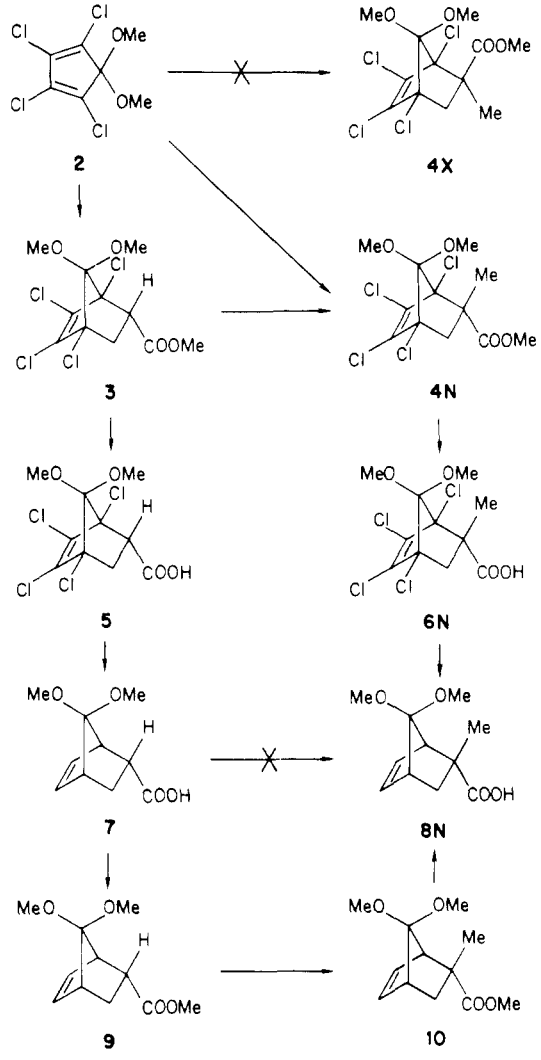
proach to **1** employed 5,5-dimethoxytetrachlorocyclopentadiene (**2**) as the diene component of a Diels–Alder reaction.[3] A standard difficulty in such additions is that



the bulky geminal groups in the diene interfere sterically with the larger group(s) in the dienophile and enforce endo stereochemistry on the product.[4,5] Thus the reaction of methacrylate esters with **2** was anticipated to give low ratios of *exo*- to *endo*-carboxylates.[4a,6] To test this and to provide authentic endo materials, needed later for comparison with the exo compounds we desired, we carried out the reaction of methyl methacrylate with **2**[7] and obtained **4N** in 86% yield but could isolate none of the exo-epimer **4X** we also desired (Scheme I). The *endo*-carbomethoxy configuration in **4N** was confirmed by single-crystal X-ray analysis (Figure 1).[8]

In such bicycloheptane adducts which are derived from simple acrylates, it is not clear from drawings or models which is the more hindered side of the molecule,[9] but we initially hoped to be able to methylate these materials from the endo direction to produce **4X**. The result of methylation of **3**[3c] however was a 76% yield of material identical in every respect with **4N** prepared by direct Diels–Alder reaction. As an alternative, it appeared quite possible that removal of the chlorine from the system might diminish

Scheme I



steric hindrance to approach from the endo side more than it would affect exo approach. Therefore compound **3** was saponified in high yield to give **5**,[3b,c,10] which was dehalogenated, using sodium in liquid ammonia, to provide **7**[10] in 93% yield. When direct alkylation of **7** by means of its dianion failed in several attempts,[11] the corresponding methyl ester **9** was utilized. However methylation of **9** gave **10** in 36% yield as the sole isolatable alkylated product, identified by comparison with material derived from **4N**.

Although by some measures of volume a nitrile group is about 20% larger than a methyl,[12] the nitrile is smaller in some dimensions because of its slim linear shape, so that the addition of methacrylonitrile to **2** has been reported to give a more favorable exo/endo ratio of 2.3:1.[4a] We therefore repeated this reaction and have confirmed both the above general result (ratio 3.5:1 in our hands) and the stereochemical assignments of the products (Scheme II), apparently made earlier solely on spectroscopic evidence.

(3) (a) Newcomer, J. S.; McBee, E. T. *J. Am. Chem. Soc.* **1949**, *71*, 946. (b) McBee, E. T.; Dively, W. R.; Burch, J. E. *Ibid.* **1955**, *77*, 385. (c) Jung, M. E.; Hudspeth, J. P. *Ibid.* **1977**, *99*, 5508 and references cited therein.

(4) (a) Mark, V. *J. Org. Chem.* **1974**, *39*, 3181. (b) Jung, M. E.; Radcliffe, C. D. *Tetrahedron Lett.* **1980**, *21*, 4397.

(5) However, see ref 3c and Jung, M. E.; Light, L. A. *J. Org. Chem.* **1982**, *47*, 1084.

(6) Cf. Meek, J. S.; Trapp, W. B. *J. Am. Chem. Soc.* **1957**, *79*, 3909.

(7) Kron, V. A.; Kron, E. M.; Stepanov, D. E.; Kalabina, A. V. *Izv. Nauch.-Issled. Inst. Nefte-Uglekhim. Sin. Irkutsk. Univ.* **1969**, *11* (Pt. 1), 68; *Chem. Abstr.* **1973**, *78*, 3776d.

(8) X-ray data previously collected in this department were afterward analyzed by one of us (R.A.L.) while on sabbatical leave in California, using computational facilities generously made available by Nicolet XRD Corp. Figure 1 was subsequently used by Nicolet, with our permission, for a display at the spring, 1981, Pittsburgh Conference, and then appeared, with attribution inadvertently omitted, in Nicolet advertisements in *Chem. Eng. News* **1981**, *59* (12), 67 and (30), 91.

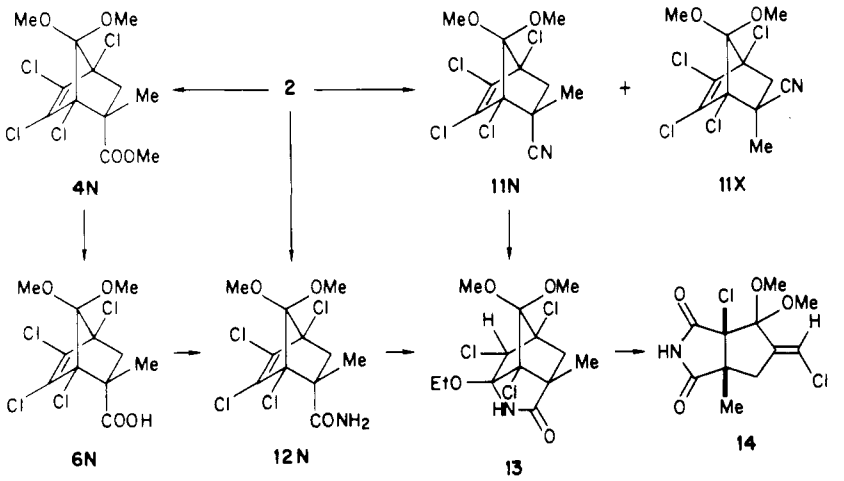
(9) Garrat, P. J.; Hollowood, F. *J. Org. Chem.* **1982**, *47*, 68.

(10) Menger, F. M.; Glass, L. E. *J. Am. Chem. Soc.* **1980**, *102*, 5404. Menger, F. M. *Tetrahedron* **1983**, *39*, 1013.

(11) The *exo*-carboxyl epimer **8X** is reported as the product of this alkylation in ref 10, where it is mentioned (with no experimental details) as part of a longer sequence giving a "low" overall yield. Evidently the immediate product of the alkylation in ref 10 was not isolated but was carried forward as a mixture for several steps to facilitate the eventual separation of what was apparently a very minor component. We were unable to isolate any methylated carboxylic acid directly from this alkylation mixture.

(12) Quayle, O. R. *Chem. Rev.* **1953**, *53*, 439.

Scheme II

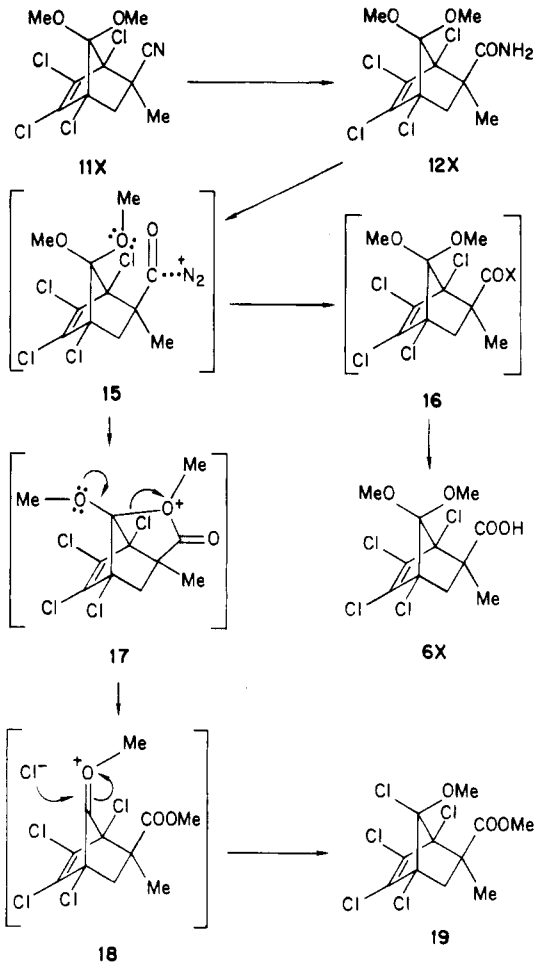


The nitrile assigned the endo configuration (**11N**, mp 85–7 °C) has now been related chemically to the ester **4N** through an extensive rearrangement dependent upon its endo stereochemistry, a sequence we have reported elsewhere (Scheme II).[13]

We have also confirmed the stereochemistry assigned to the major product of the Diels–Alder reaction, the *exo*-nitrile **11X** (mp 68–70 °C), by demonstrating interaction of the 2-exo function with the 7-ketone. This nitrile was hydrolyzed under basic conditions to the carboxamide **12X** (Scheme III), but all attempts at further base hydrolysis returned only unchanged amide. Although we had wished to avoid acidic conditions in order to preserve the 7-ketal, ultimately this amide hydrolysis was accomplished by treatment with *n*-butyl nitrite and dry HCl in acetic acid.[14] This procedure provided a 70% yield of the anticipated tetrachloro carboxy ketal **6X** but gave in addition 13% of neutral crystalline material containing *five* chlorine atoms. The analytical and spectral data of this compound are consistent with structure **19**, which we suggest to have arisen by the sequence shown in Scheme III.

The metal–ammonia dechlorination of our system[4b] would be expected to result in accompanying reduction of the exo functional group if it were attempted with **11X** or **12X**.[15] When carried out with *exo*-carboxylic acid **6X**, it gave a 98% crude yield of dehalogenated material with all other functions intact (**8X**, Scheme IV). Catalytic hydrogenation proceeded smoothly and very rapidly, as is common with these strained olefins,[16] giving a nearly quantitative yield of saturated carboxy ketal **20**. Treatment of **20** with acid in aqueous THF gave an 86% yield of crystalline product whose IR spectra (KBr, CH_2Cl_2, Et_2O) indicate that it is not the keto acid **21** but its ring-chain tautomer, the hydroxy lactone **22**. The angular compression at C7 in bicycloheptanes (ca. 94°)[17] which destabilizes trigonal hydridization and makes C7 ketal

Scheme III



functions more difficult than usual to hydrolyze also renders a C7 carbonyl particularly susceptible to addition, strongly favoring **22** in this equilibrium.[5,19] This may be contrasted with the reported situation of 7-*syn*-carboxynorbornanone (**23**) and several of its derivatives, in which the positions of these two functions are reversed, and in which apparently the keto acid form strongly predominates.[20] Further evidence of this tendency at C7 appears

(13) Thompson, H. W.; Wong, J. K. *J. Org. Chem.* **1985**, *50*, 404.
(14) Sperber, N.; Papa, D.; Schwenk, E. *J. Am. Chem. Soc.* **1948**, *70*, 3091.
(15) Watt, G. W. *Chem. Rev.* **1950**, *46*, 317. Smith, M. In "Reduction"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968; pp 95–170.
(16) Turner, R. B.; Meador, W. R.; Winkler, R. E. *J. Am. Chem. Soc.* **1957**, *79*, 4116.
(17) Wilcox, C. F. *J. Am. Chem. Soc.* **1960**, *82*, 414. Apgar, P. A.; Ludwig, M. L. *Ibid.* **1972**, *94*, 964 and references cited therein. Chadwick, D. J.; Whittleton, S. N.; Small, R. W. H. *J. Chem. Soc., Perkin Trans. 2* **1982**, 669.
(18) (a) Vogel, E.; Wyes, E.-G. *Chem. Ber.* **1965**, *98*, 3680. (b) Schuda, P. F.; Ammon, H. L.; Heimann, M. R.; Bhattacharjee, S. *J. Org. Chem.* **1982**, *47*, 3434. Fuchs, B.; Zizuashvili, J.; Abramson, S. *Ibid.* **1982**, *47*, 3474.
(19) (a) McBee, E. T.; Stoffer, J. O.; Braendlin, H. P. *J. Am. Chem. Soc.* **1962**, *84*, 4540. (b) Cf. Tanida, H.; Nishiya, T.; Irie, T. *J. Org. Chem.* **1979**, *44*, 3337. Irie, T.; Tanida, H. *Ibid.* **1980**, *45*, 1795, in which apparently only solution IR spectra were obtained.

in the behavior of ketal ester **24**, made by diazomethane treatment of **20**. Several attempts to produce keto ester **25** by selective hydrolysis of **24** gave only **22**. We attribute this to internal attack by the hydrate of the 7-ketone[18a,19b] upon the protonated ester, which is sufficiently hindered that external attack would be expected to be quite slow.

Although an ether solution of lactol **22** appeared to contain a negligible concentration of **21** (IR), direct treatment with diazomethane provide an 88% yield of keto ester **25**, presumably by continuous displacement of the equilibrium as a low concentration of **21** was consumed.[21] Standard Wittig conditions then converted **25** to **26** in 46% yield. Alternatively when **22** was treated directly with 2 equiv of Wittig reagent, **27** was formed in essentially quantitative yield, undoubtedly through initial reversion to the keto carboxylate. Diazomethane treatment of **27** again produced **26**.

Experimental Section[22]

Diels–Alder Preparation of 7,7-Dimethoxy-2-*exo*-methyl-2-*endo*-carbomethoxy-1,4,5,6-tetrachlorobicyclo-[2.2.1]hept-5-ene (4N)[7] (Method A). A mixture of 15.0 g (56.8 mmol) of **2** and 11.4 g (113.6 mmol) of methyl methacrylate was stirred under N_2 and heated at 110 °C for 48 h. After excess dienophile was removed in vacuo, cooling the yellowish reaction mixture produced a crude solid, recrystallized from hexane to give 18.0 g (86%) of **4N**: mp 100–102 °C (lit.[7] mp 96–97 °C); MS, *m/e* (relative intensity) 366.1 (M^+, 0.18), 364.1 (M^+, 0.21), 362.1 (M^+, 0.18), 333.1 (8.8), 331.1 (45.8), 329.1 (97.7), 327.1 (100); IR (Nujol) 1730, 1600 cm^{-1}; ^1H NMR δ 3.63 (3 H, s), 3.57 (3 H, s), 3.51 (3 H, s), 2.92 (1 H, d, J = 12 Hz), 2.17 (1 H, d, J = 12 Hz), 1.60 (3 H, s).

Anal. Calcd for $C_{12}H_{14}Cl_4O_4$: C, 39.59; H, 3.88; Cl, 38.96. Found: C, 39.56; H, 3.83; Cl, 38.22.

Diels–Alder Preparation of 7,7-Dimethoxy-2-*endo*-carbomethoxy-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-ene (3).[3c] A mixture of 10.0 g (37.9 mmol) of **2** and 3.27 g (37.9 mmol) of methyl acrylate was heated at 75 °C under argon with stirring for 48 h. Distillation gave 12.8 g (97%) of **3** as a colorless liquid: bp 120–125 °C at 1.0 mm; MS, *m/e* (relative intensity) 356.2 (M^+, 0.07), 354.1 (M^+, 0.17), 352.1 (M^+, 0.33), 350.2 (M^+, 0.55), 348.2 (M^+, 0.45), 319.1 (13.4), 317.2 (38.6), 315.2 (100), 313.3 (98.7); IR (neat) 1730, 1600 cm^{-1}; ^1H NMR δ 3.72 (3 H, s), 3.64 (3 H, s), 3.58 (3 H, s), 3.40 (1 H, dd, J = 9, 4.5 Hz), 2.53 (1 H, dd, J = 12, 9 Hz, H_{3X}), 2.23 (1 H, dd, J = 12, 4.5 Hz, H_{3N}).

Anal. Calcd for $C_{11}H_{12}Cl_4O_4$: C, 37.74; H, 3.46; Cl, 40.52. Found: C, 37.51; H, 3.23; Cl, 39.90.

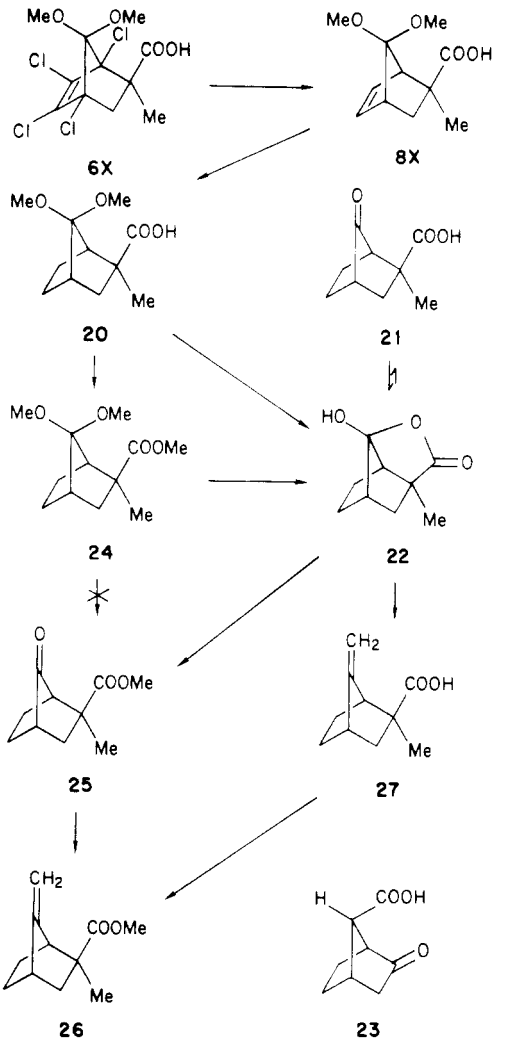
Preparation of Compound 4N by Alkylation of 3 (Method B). A solution of LDA was prepared by dropwise addition of a solution of *n*-BuLi which was 1.6 M in hexane (1.79 mL, 2.86 mmol) to a solution of 0.40 mL (2.86 mmol) of *i*-Pr_2NH in 0.7 mL of dry THF cooled with an ice bath. After being stirred at 0 °C for 20 min, the yellowish solution was further cooled to −78 °C and 1.0 g (2.86 mmol) of compound **3** in 1 mL of THF was added dropwise. The mixture was stirred for 30 min, and 0.18 mL (2.86 mmol) of MeI was added by syringe. After the reaction mixture was stirred while being warmed to room temperature, the usual extraction and isolation procedure provided 1.0 g of crude solid. This was recrystallized from hexane to give 800 mg (76%) of compound **4N**: mp 99–100 °C, mixed mp 99–101 °C; ^1H NMR superimposable with that of **4N** described above. A single-crystal X-ray determination provided the structure shown in Figure 1.[8]

Saponification of 3 To Give 7,7-Dimethoxy-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic Acid (5).[3b,c] Compound **3** (7.2 g, 20.5 mmol) in 200 mL of 1:1 EtOH/water was refluxed with 6.0 g (107 mmol) of KOH for 45 min under argon. After solvent had been partially removed under vacuum, the residue was diluted with saturated oxalic acid. The usual extraction and isolation procedure afforded 6.84 g (99%) of **5** as a white solid. Recrystallization from Et_2O/hexane gave pure material: mp 164–165 °C (lit.[3c,b] 163 °C, 163–164 °C); MS, *m/e* (relative intensity) 338.0 (M^+, 0.13), 336.0 (M^+, 0.21), 334.1 (M^+, 0.17), 305.0 (5.2), 303.1 (33.2), 301.1 (97.2), 299.1 (100); IR (Nujol) 3400–2400, 1700, 1605 cm^{-1}; ^1H NMR δ 9.50 (1 H, s, br, exch with D_2O), 3.68 (3 H, s), 3.60 (3 H, s), 3.41 (1 H, dd, J = 9, 4.5 Hz), 2.42 (1 H, dd, J = 12, 9 Hz, H_{3X}), 2.31 (1 H, dd, J = 12, 4.5 Hz, H_{3N}).

Anal. Calcd for $C_{10}H_{10}Cl_4O_4$: C, 35.75; H, 3.00; Cl, 42.21. Found: C, 35.91; H, 2.92; Cl, 41.63.

Dehalogenation of 5 To Give 7,7-Dimethoxybicyclo-[2.2.1]hept-5-ene-2-*endo*-carboxylic Acid (7).[3c] Sodium (4.1 g, 179 mmol) in small pieces was dissolved in 75–100 mL of anhydrous liquid NH_3. A solution of compound **5** (3.0 g, 8.9 mmol) in 48 mL of 1:1 absolute EtOH/Et_2O was added dropwise over 20 min. After this addition, the mixture was stirred for another 20 min. Solid NH_4Cl was added in portions until the mixture

Scheme IV



(20) Beckmann, S.; Geiger, H.; Schaber-Kiechle, M. *Chem. Ber.* **1959**, *92*, 2419. Beckmann, S.; Geiger, H. *Ibid.* **1961**, *94*, 48.

(21) Frimer, A. A.; Gilinsky-Sharon, P.; Aljadeff, G. *Tetrahedron Lett.* **1982**, *23*, 1301.

(22) Melting points were determined with a Thomas-Hoover Uni-Melt apparatus and are uncorrected, as are boiling points. IR spectra were taken with Perkin-Elmer 727B, 1320, or 180 IR spectrometers. ^1H NMR spectra were recorded at 60, 79.5, and 90 MHz with Varian T60A, CF-T-20, and EM-390 spectrometers, respectively, and at 100 MHz with a Varian XL-100 or a JEOL JNM-PS-FT-100 spectrometer, utilizing $CDCl_3$ ($SiMe_4$) as the solvent. ^{13}C NMR spectra were recorded at 20 and 25.16 MHz with Varian FT-80A and XL-100 spectrometers, respectively, utilizing $CDCl_3$ as solvent unless otherwise specified. Low- and high-resolution mass spectra were determined with Varian CH-5 and MAT 312 spectrometers, respectively. Data for the single-crystal X-ray structure determination of compound **4N** were collected with a Syntex Model $P2_1$ automatic X-ray diffractometer. Elemental analyses were carried out with a Perkin-Elmer 240 elemental analyzer (C, H, N) and an American Instrument Co. chloride titrator. E. Merck G60 and Baker 60–200 mesh SiO_2 were used for preparative and flash column chromatography, respectively.

turned white. After removal of NH_3 by passing N_2 through the mixture, ice–water was added, and the mixture was acidified with 2 N HCl. The usual extraction and isolation procedure afforded 1.7 g (93%) of compound **7**: mp 83.5–85 °C (lit.[3c] mp 78–79 °C); MS, *m/e* (relative intensity) 199.1 (4.5), 198.1, (M^+, 37.6), 167.1 (11.6), 154.1 (10.2), 153.1 (100); IR (Nujol) 3400–2400, 1690, 1575 cm^{-1}; ^1H NMR δ 9.20 (1 H, br, exch with D_2O), 6.31 (2 H, m), 3.31 (3 H, s), 3.23 (3 H, s), 3.20 (1 H, overlapped with OMe), 2.90 (1 H, m), 2.19 (2 H, m), 1.43 (1 H, dd, J = 12, 4 Hz, H_{3N}).

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.67; H, 6.95.

Esterification of 7 To Give 7,7-Dimethoxy-2-*endo*-carbomethoxybicyclo[2.2.1]hept-5-ene (9). Compound **7** (4.0 g, 20.2 mmol) was treated with CH_2N_2 in Et_2O. After the reaction was complete, excess CH_2N_2 and Et_2O were removed by gently passing in N_2 gas and pumping under vacuum. Distillation gave 4.1 g (98%) of **9** as a colorless liquid: bp 70–75 °C (bath temperature) at 2.5 mm; $n_D^{25.8}$ 1.4725; MS, *m/e* (relative intensity) 213.2 (6.1), 212.1 (M^+, 49.2), 153.1 (100); IR (neat) 3060, 1730, 1580 cm^{-1}; ^1H NMR δ 6.13 (2 H, m), 3.62 (3 H, s), 3.22 (3 H, s), 3.14 (3 H, s), 3.13 (1 H, overlapped with OMe), 2.82 (1 H, m), 2.10 (2 H, complex), 1.40 (1 H, dd, J = 12, 4 Hz, H_{3N}).

Alkylation of 9 To Give 7,7-Dimethoxy-2-*exo*-methyl-2-*endo*-carbomethoxybicyclo[2.2.1]hept-5-ene (10). Compound **9** (1.0 g, 4.7 mmol) was alkylated with MeI in the presence of LDA as a base, as previously described for the conversion of **3** to **4N**. Chromatography afforded 380 mg (36%) of compound **10**: ^1H NMR δ 6.12 (2 H, m), 3.62 (3 H, s), 3.22 (3 H, s), 3.18 (3 H, s), 2.80 (2 H, m), 2.05 (1 H, d, J = 12 Hz), 1.71 (1 H, dd, J = 12, 4 Hz, H_{3N}), 1.55 (3 H, s).

Saponification of 10 To Give 7,7-Dimethoxy-2-*exo*-methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic Acid (8N) (Method A). Compound **10** (380 mg, 1.7 mmol) in 20 mL of 4:1 EtOH/water was refluxed with 860 mg (15.4 mmol) of KOH for 36 h. Ice–water was added, and the mixture was extracted with Et_2O. The basic aqueous layer was acidified with oxalic acid and subjected to the usual extraction and isolation procedure, which afforded 235 mg (65%) of compound **8N**: mp 104.5–106.5 °C; mixed mp with a sample prepared by method B, described below, undepressed; ^1H NMR superimposable with that of a sample produced by method B.

Saponification of 4N To Give 7,7-Dimethoxy-2-*exo*-methyl-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic Acid (6N). Compound **4N** (4.0 g, 11.0 mmol) was refluxed with 6.0 g (107 mmol) of KOH in 80 mL of 7:3 EtOH/water for 1 h. After EtOH was removed under vacuum, the residue was diluted with 500 mL of water and extracted once with Et_2O. The aqueous phase was acidified with oxalic acid and subjected to the usual extraction and isolation procedure, which afforded 3.2 g (82%) of compound **6N** as a white solid. Recrystallization from Et_2O/petroleum ether gave a sample: mp 155.5–157.5 °C; IR (Nujol) 2800–2300, 1700, 1600 cm^{-1}; ^1H NMR δ 8.50 (1 H, br, exch with D_2O), 3.60 (3 H, s), 3.42 (3 H, s), 2.88 (1 H, d, J = 12 Hz), 2.18 (1 H, d, J = 12 Hz), 1.68 (3 H, s).

Anal. Calcd for $C_{11}H_{12}Cl_4O_4$: C, 37.74; H, 3.46; Cl, 40.52. Found: C, 37.60; H, 3.39; Cl, 40.20.

Preparation of Compound 8N by Dehalogenation of 6N (Method B). In a procedure similar to that used for preparation of **7**, a solution of 6.0 g (17.1 mmol) of compound **6N** was dehalogenated by using 8.0 g (350 mmol) of Na. The workup previously described afforded 4.0 g (95%) of crude yellowish solid. Recrystallization from Et_2O/petroleum ether afforded pure **8N** as white crystals: mp 105–107 °C; MS, *m/e* (relative intensity) 213.1 (9.5), 212.1 (M^+, 78.3), 197.1 (12.6), 167.1 (100); IR (Nujol) 2800–2350, 1690, 1580 cm^{-1}; ^1H NMR δ 9.50 (1 H, br, exch with D_2O), 6.14 (2 H, m), 3.22 (3 H, s), 3.12 (3 H, s), 2.80 (2 H, m), 2.09–1.68 (2 H, m), 1.59 (3 H, s).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.47; H, 7.38.

Diels–Alder Preparation of 7,7-Dimethoxy-2-methyl-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-ene-2-carbonitriles 11X and 11N. A mixture of 10.0 g (37.9 mmol) of **2** and 5.1 g (75.8 mmol) of methacrylonitrile was stirred and heated under N_2 with an oil bath at 125 °C for 24–26 h. Excess dienophile was removed in vacuo, and the product was chromatographed. Elution with 4:1 hexane/Et_2O afforded two materials.

The isomer eluted first (R_f 0.46 on TLC with the above solvent) and subsequently shown to be the *exo*-nitrile **11X** was obtained initially as a liquid, which crystallized from petroleum ether to give 9.2 g (73%) of white crystals: mp 68–70 °C; MS, *m/e* (relative intensity) 335.1 (M^+, 0.17), 333.1 (M^+, 0.60), 331.1 (M^+, 1.14), 329.1 (M^+, 0.88), 296.1 (96.6), 294.1 (100); IR (Nujol) 2250, 1600, cm^{-1}; ^1H NMR δ 3.70 (3 H, s), 3.60 (3 H, s), 2.94 (1 H, d, J = 12 Hz, H_{3X}), 1.89 (1 H, d, J = 12 Hz, H_{3N}) 1.31 (3H, s).

Anal. Calcd for $C_{11}H_{11}Cl_4NO_2$: C, 39.91; H, 3.35; Cl, 42.84; N, 4.23. Found: C, 40.09; H, 3.33; Cl, 42.18; N, 4.15.

The second-eluted isomer, subsequently shown to be the *endo*-nitrile **11N**, had R_f 0.43 on TLC and was obtained as a solid and recrystallized from hexane to give 2.6 g (21%) of white crystals: mp 85–87 °C; MS, *m/e* (relative intensity) 333.1 (M^+, 0.19), 331.0 (M^+, 0.34), 329.0 (M^+, 0.24), 296.1 (95.5), 294 (100); IR (Nujol) 2250, 1600 cm^{-1}; ^1H NMR δ 3.53 (3 H, s), 3.50 (3 H, s), 2.45 (2 H, s, degenerate AB), 1.75 (3 H, s).

Anal. Calcd for $C_{11}H_{11}Cl_4NO_2$: C, 39.91; H, 3.35; Cl, 42.84; N, 4.23. Found: C, 39.56; H, 3.30; Cl, 42.41; N, 4.23.

Conversion of 6N to 7,7-Dimethoxy-2-*exo*-methylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxamide (12N).[13] Compound **12N**, previously prepared by Diels–Alder reaction of **2** with methacrylamide[13] was also prepared as follows.

1,1′-Carbonyldiimidazole (493 mg, 3.0 mmol) was added to a stirred solution of 970 mg (2.8 mmol) of compound **6N** in 10 mL of dry DMF. The reaction mixture was warmed at 35 °C for 3 h and then cooled; 2 mL of DMF saturated with NH_3 was added, and the mixture was allowed to warm to room temperature and stirred for another 30 min. The reaction was diluted with ice–water, whereupon the usual extraction and isolation procedure afforded 450 mg (47%) of solid **12N**. Recrystallization from Et_2O/hexane gave an analytically pure sample, mp 177–178 °C, which was identical with the sample previously described.[13]

Basic Conversion of 11N to 3a-Chloro-(*E*)-5-(chloromethylene)-4,4-dimethoxy-6a-methyl-*cis*-tetrahydrocyclopenta[*c*]pyrrole-1,3-(2*H*,3a*H*)-dione (14).[13] A mixture of compound **11N** (2.0 g, 6.0 mmol) and 5.0 g (89 mmol) of KOH in 60 mL of 5:1 EtOH/water was refluxed under N_2 for 3 days. The residue remaining after concentration of the dark mixture was diluted with ice–water and extracted with Et_2O three times. The aqueous layer was then acidified with either oxalic acid or dilute HCl and subjected to the usual extraction and isolation procedure, affording a crude solid recrystallized from *i*-Pr_2O to give 880 mg (49%) of white crystals, mp 179–181 °C, identical in every respect with the samples of **14** described previously.[13]

Basic Hydrolysis of 11X To Give 7,7-Dimethoxy-2-*endo*-methyl-1,4,5,6-tetrachlorobicyclo[2.2.1]hept-5-ene-2-*exo*-carboxamide (12X). To a stirred solution of 50 g (0.15 mol) of the exo nitrile **11X** in 350 mL of EtOH was added a solution of 75 g (1.34 mol) of KOH in 150 mL of water. After the mixture was refluxed for 72 h and concentrated, addition of water followed by the usual extraction and isolation procedure afforded a crude solid, which was decolorized and recrystallized from *i*-Pr_2O to give 41.9 g (79%) of white crystals: mp 144–146 °C; MS, *m/e* (relative intensity) 318.1 (4.4), 314.1 (91.2), 312.2 (92.3), 269.1 (40.9), 59.1 (100); IR (Nujol) 3460, 1660, 1600 cm^{-1}; ^1H NMR δ 6.35–5.85 (2 H, br, exch with D_2O), 3.60 (3 H, s), 3.58 (3 H, s), 3.57 (1 H, d, J = 12 Hz, H_{3X}), 1.74 (1 H, d, J = 12, H_{3N}), 1.25 (3 H, s).

Anal. Calcd for $C_{11}H_{13}Cl_4NO_3$: C, 37.85; H, 3.75; Cl, 40.63; N, 4.01. Found: C, 37.59; H, 3.79; Cl, 40.64; N, 3.96.

***n*-Butyl Nitrite–HCl Treatment of 12X To Give 7,7-Dimethoxy-2-*endo*-methyl-1,4,5,6-tetrachlorobicyclo[2.2.1]-hept-5-ene-2-*exo*-carboxylic Acid (6X).** Anhydrous HCl was gently bubbled for 30 min into a stirred solution of 46.9 g (0.13 mol) of **12X** in 170 mL of HOAc in a 500-mL flask fitted with a gas-inlet tube, addition funnel, and reflux condenser. Then 27.8 g (0.27 mol) of *n*-butyl nitrite was added dropwise over 30 min to the stirred solution, which became deep red; within 10–15 min gas evolution was observed. After addition was complete, the solution was stirred at room temperature for 2 h and then on the steam bath for 2 h. Volatiles were removed in vacuo, and the residue was dissolved in 10% KOH solution. The usual extraction and isolation procedure afforded a neutral fraction of 14.2 g. Acidification of the alkaline solution and reextraction then led to 33.0 g (70%) of the *exo*-acid **6X**. Recrystallization from *i*-Pr_2O/hexane gave analytically pure white crystals: mp 171–173

°C; MS, m/e (relative intensity) 319.1 (4.1), 315.1 (94.9), 313.1 (100); IR (Nujol) 3300–2500, 1690, 1605 cm^{-1}; ^1H NMR δ 10.70 (1 H, s, br, exch with D_2O), 3.75 (3 H, s), 3.52 (3 H, s), 3.28 (1 H, d, J = 12 Hz, H_{3X}), 1.77 (1 H, d, J = 12 Hz, H_{3N}), 1.30 (3 H, s).

Anal. Calcd for $C_{11}H_{12}Cl_4O_4$: C, 37.74; H, 3.46; Cl, 40.52. Found: C, 37.58; H, 3.74; Cl, 40.40.

7-Methoxy-2-*endo*-methyl-2-*exo*-carbomethoxy-1,4,5,6,7-pentachlorobicyclo[2.2.1]hept-5-ene (19). The neutral fraction of 14.2 g obtained above was chromatographed on SiO_2 and eluted with 4:1 hexane/EtOAc to give 6.4 g (13%) of compound **19** and 5.6 g (12%) of the starting material **12X**. Recrystallization of **19** analytically pure white crystals: mp 91–93 °C; MS, m/e (relative intensity) 372.1 (M^+, 0.30), 370.1 (M^+, 1.06), 368.1 (M^+, 1.5), 366.2 (M^+, 0.94), 337.1 (15.6), 335.1 (50.7), 333.1 (100), 331.1 (76.5), 273.1 (25.7), 271.2 (22.2); IR (Nujol) 1730, 1610 cm^{-1}; ^1H NMR δ 3.75 (3 H, s), 3.65 (3 H, s), 3.37 (1 H, d, J = 12 Hz, H_{3X}), 1.89 (1 H, d, J = 12 Hz, H_{3N}), 1.30 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 172.0, 133.5, 131.2, 115.9, 83.0, 76.2, 54.8, 54.3, 52.5, 45.1, 22.3.

Anal. Calcd for $C_{11}H_{11}Cl_5O_3$: C, 35.85; H, 3.01; Cl, 48.11. Found: C, 35.99; H, 2.96; Cl, 48.18.

Esterification of 6X To Give 7,7-Dimethoxy-2-*endo*-methyl-2-*exo*-carbomethoxy-1,4,5,6-tetrachlorobicyclo-[2.2.1]hept-5-ene (4X). Treatment of 1.50 g (4.29 mmol) of **6X** in Et_2O with CH_2N_2, as previously described for the conversion of **7** to **9**, yielded crude product, purified by preparative TLC to give 1.30 g (83%) of **4X** as white crystals: mp 68–70 °C; MS, m/e (relative intensity) 364.3 (M^+, 0.05), 362.3 (M^+, 0.06), 331.2 (21.4), 329.2 (60.2), 327.3 (63.5), 269.2 (13.1), 267.2 (13.7), 159.1 (12.6), 75.1 (18.5), 59.1 (100); IR 1720, 1605 cm^{-1}; ^1H NMR δ 3.77 (3 H, s), 3.55 (3 H, s), 3.48 (3 H, s), 3.33 (1 H, d, J = 11 Hz, H_{3X}), 1.77 (1 H, d, J = 11, H_{3N}), 1.21 (3 H, s).

Anal. Calcd for $C_{12}H_{14}Cl_4O_4$: C, 39.59; H, 3.88; Cl, 38.96. Found: C, 39.66; H, 3.85; Cl, 39.12.

Dehalogenation of 6X To Give 7,7-Dimethoxy-2-*endo*-methylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic Acid (8X). A solution was prepared by gradual addition of 23.4 g (1.02 mol) of Na to 500 mL of anhydrous liquid NH_3. A solution of 21.0 g (0.06 mol) of compound **6X** in a mixture of 100 mL of absolute EtOH and 130 mL of anhydrous Et_2O was then added dropwise over 30 min and stirred for another 30 min. Then solid NH_4Cl was added in portions until the reaction mixture turned white. After evaporation of NH_3, addition of water, and acidification with 10% aqueous HCl, the usual extraction and isolation procedure afforded 12.5 g (98%) of **8X** as a crude solid. Recrystallization from hexane gave analytically pure white crystals: mp 108–110 °C; MS, m/e (relative intensity) 213.3 (14.8), 212.1 (M^+, 97.9), 197.0 (33.7), 181 (38.6), 168 (22.3), 100 (100); IR (KBr) 3600–2450, 1700, 1580 cm^{-1}; ^1H NMR δ 12.46 (1 H, br, exch with D_2O), 6.22 (2 H, m), 3.27 (1 H, m), 3.18 (3 H, s), 3.17 (3 H, s), 2.82 (1 H, m), 2.64 (1 H, dd, J = 12 Hz, 4 Hz, H_{3X}), 1.16 (3 H, s), 0.88 (1 H, d, J = 12 Hz, H_{3N}).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.05; H, 7.51.

Catalytic Hydrogenation of 8X To Give 7,7-Dimethoxy-2-*endo*-methylbicyclo[2.2.1]heptane-2-*exo*-carboxylic Acid (20). Compound **8X** (2.17 g, 10.2 mmol) in 60 mL of MeOH was shaken with 200 mg of 5% Pd/C in a Parr apparatus under H_2. After the theoretical amount of H_2 had been taken up (in about 5 min), an additional 5 min of shaking produced no further pressure drop. The usual isolation procedure provided 2.11 g (96%) of **20** as white granular crystals. Recrystallization from petroleum ether gave an analytically pure sample: mp 88–89 °C; MS, m/e (relative intensity) 215.2 (2.7), 214.2 (M^+, 21.7), 199.1 (18.5), 183.1 (19.0), 170.1 (13.7), 169.1 (100), 159.1 (32.2), 101.1 (91.3); IR (KBr) 3600–2450, 1700 cm^{-1}; ^1H NMR δ 10.5 (1 H, br, exch with D_2O), 3.28 (3 H, s), 3.19 (3 H, s), 2.51 (2 H, complex), 2.05 (1 H, complex), 1.80–1.51 (3 H, complex), 1.42 (3 H, s), 1.07 (1 H, complex), 0.98 (1 H, d, J = 12 Hz, H_{3N}).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.87; H, 8.43.

Ketal Hydrolysis of 20 To Give Hexahydro-6a-hydroxy-3-methyl-3,6-methano-2*H*-cyclopenta[*b*]furan-2-one (22). Concentrated HCl (24 mL) was added dropwise to a solution of 6.0 g (28.0 mmol) of compound **20** in 72 mL of THF and 60 mL of water at ice-bath temperature. After being allowed to stir at room temperature for 4 days, the mixture was poured into ca. 1.5 L of ice-water. The usual extraction and isolation procedure afforded 4.50 g (86%) of lactol **22** as granular white crystals: mp 109–111 °C; MS, m/e (relative intensity), 169.1 (0.63), 168.1 (M^+, 1.47), 140.1 (25.8), 126.1 (18.9), 122.1 (22.8), 111.0 (15.2), 96.1 (56.0), 95.1 (100); IR (KBr) 3420, 1760 cm^{-1}; ^1H NMR δ 5.42 (1 H, br, exch with D_2O), 2.30–1.38 (7 H, complex), 1.20 (3 H, s), 1.19 (1 H, d, J = 12 Hz); ^{13}C NMR δ 180.0, 115.0, 54.2, 50.6, 41.2, 37.0, 30.6, 17.5, 12.1.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.19.

Esterification of 20 To Give 7,7-Dimethoxy-2-*endo*-methyl-2-*exo*-carbomethoxybicyclo[2.2.1]heptane (24). Treatment of 12.64 g (59.0 mmol) of compound **20** in Et_2O with ethereal CH_2N_2, as previously described for conversion of **7** to **9**, led to isolation of 12.24 g (91%) of compound **24**: bp 64–68 °C at 0.1 mm; $n_D^{26.8}$ 1.4634; MS, m/e (relative intensity) 229.1 (2.0), 228.1 (M^+, 15.0), 213.1 (14.3), 197.1 (28.2), 173.0 (35.3), 169.1 (100); IR (neat) 1720 cm^{-1}; ^1H NMR δ 3.66 (3 H, s), 3.22 (3 H, s), 3.12 (3 H, s), 2.60 (2 H, complex), 2.01 (1 H, m), 1.85–1.30 (4 H, m); 1.20 (3 H, s), 0.92 (1 H, d, J = 12 Hz).

When 1.0 g (4.4 mmol) of compound **24** was stirred with 8 mL of concentrated HCl, 24 mL of THF, and 20 mL of water for 40 h, workup as described above for the hydrolysis of **20** gave 627 mg (85%) of **22**, identical with that previously obtained from **20**.

Esterification of 22 To Give 2-*endo*-Methyl-2-*exo*-carbomethoxy-7-oxobicyclo[2.2.1]heptane (25). Treatment of 1.5 g (8.9 mmol) of compound **22** in 25 mL of Et_2O with ethereal CH_2N_2, as previously described for conversion of **7** to **9**, led to an oil distilled at 1.0 mm (55–60 °C bath temperature) to yield 1.6 g (88%) of **25**; $n_D^{26.3}$ 1.4757; MS, m/e (relative intensity) 183.1 (0.10), 182.2 (M^+, 0.41), 154.1 (20.2), 122.1 (20.1), 95.1 (83.5), 79.0 (32.4), 43.0 (100); exact mass calcd for $C_{10}H_{14}O_3$ m/e 182.1068, found 182.1052; IR (neat) 1760, 1725 cm^{-1}; ^1H NMR δ 3.64 (3 H, s), 2.61–1.50 (7 H, complex), 1.37 (3 H, s), 1.26 (1 H, d, J = 12 Hz).

Wittig Reaction of 22 To Give 2-*endo*-Methyl-7-methylenebicyclo[2.2.1]heptane-2-*exo*-carboxylic Acid (27). A solution of *n*-BuLi which was 1.6 M in hexane (46.4 mL, 74.3 mmol) was added dropwise by syringe under N_2 to a stirred mixture of 26.52 g (74.0 mmol) of methyltriphenylphosphonium bromide in 180 mL of THF at ice-bath temperature over 20 min. The mixture was then stirred at room temperature until all salts were dissolved (about 1 h) and then cooled in an ice-bath. A solution of 5.68 g (33.8 mmol) of the lactol **22** in 50 mL of THF was then added over 15 min. This mixture was allowed to stir overnight and then refluxed 4 h, all under N_2. After the cooled reaction mixture was poured into ice–water and extracted with Et_2O, the aqueous phase was separated and acidified. The usual extraction and isolation procedure led to a residue which was chromatographed (60–200 mesh SiO_2) and eluted with 7:3 hexane/EtOAc to give 4.84 g (86%) of pure white crystals: mp 74–76 °C; MS, m/e (relative intensity) 167.2 (1.75), 166.2 (M^+, 2.45), 121.1 (33.1), 93.1 (41.3), 80.1 (100); IR (KBr) 3400–2400, 1700, 888 cm^{-1}; ^1H NMR δ 10.10 (1 H, exch with D_2O), 4.60 (2 H, s), 2.81–2.23 (4 H, m), 1.80–1.35 (3 H, complex), 1.30 (3 H, s), 1.01 (1 H, d, J = 12 Hz).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.42; H, 8.52.

Wittig Reaction of 25 To Give 2-*endo*-Methyl-2-*exo*-carbomethoxy-7-methylenebicyclo[2.2.1]heptane (26). Procedure A. To a solution containing 7.7 mmol of Ph_3PCH_2 generated by the procedure described above was added 1.28 g (7.0 mmol) of **25** in 1 mL of THF. The mixture was stirred overnight at room temperature, then refluxed for 2 h, and finally poured into ice–water. The usual extraction and isolation procedure afforded a residue distilled under reduced pressure to give 0.57 g (46%) of material identical with that described below.

Procedure B. Compound **27** (0.42 g, 2.53 mmol) was treated with CH_2N_2 in Et_2O solution, as previously described, to yield 0.44 g (98%) of compound **26**: bp 70–75 °C (bath temperature) at 153 mm; $n_D^{24.1}$ 1.4741; MS, m/e (relative intensity) 181.1 (0.45), 180.1 (M^+, 1.82), 121.1 (29.1), 93.1 (27.3), 80.1 (100); exact mass calcd for $C_{11}H_{16}O_2$ m/e 180.1150, found 180.1149; IR (neat) 3080,

1720, 1675, 880 cm^{-1}; ^{1}H NMR δ 4.58 (2 H, s), 3.62 (3 H, s), 2.60 (2 H, m), 2.38 (2 H, m), 1.80–1.30 (3 H, m), 1.23 (3 H, s), 1.00 (1 H, d, J = 12 Hz).

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Registry No. **2**, 2207-27-4; **3**, 64145-36-4; **4N**, 96166-47-1; **5**, 64145-42-2; **6N**, 96166-48-2; **6X**, 96194-21-7; **7**, 96166-49-3; **8N**, 96166-50-6; **8X**, 96166-51-7; **9**, 96166-52-8; **10**, 96166-53-9; **11N**, 53969-64-5; **11X**, 53969-65-6; **12N**, 94294-31-2; **12X**, 96166-54-0; **14**, 94323-92-9; **19**, 96194-22-8; **20**, 96166-55-1; **22**, 96166-56-2; **24**, 96166-57-3; **25**, 96166-58-4; **26**, 96166-59-5; **27**, 96166-60-8; CH_2=$C(CH_3)CO_2Me$, 80-62-6; CH_2=$CHCO_2Me$, 96-33-3; CH_2=$C(CH_3)CN$, 126-98-7.

Stereospecific Synthesis of (*Z*)-Tamoxifen via Carbometalation of Alkynylsilanes

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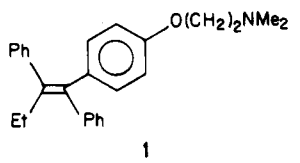
A stereospecific synthesis of (*Z*)-tamoxifen, a tetrasubstituted alkene with antiestrogenic activity, is described. The key reaction that establishes the olefin stereochemistry is a carbometalation of phenyl(trimethylsilyl)acetylene with diethylaluminum chloride–titanocene dichloride. A key intermediate that would lead to (*E*)-tamoxifen was also prepared in an analogous stereospecific manner.

(*Z*)-Tamoxifen[1,2] (1) (1 citrate = ICI-46,474, Nolvadex) is an antiestrogenic agent that inhibits the development and growth of mammary tumors in rats[3] and is effective in treating estrogen-dependent, metastatic breast cancer in humans.[4] On the other hand, (*E*)-tamoxifen, usually referred to as *cis*-tamoxifen (**2**, ICI-47,699), has no clinical



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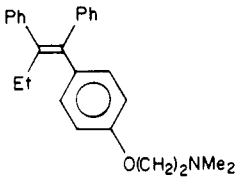


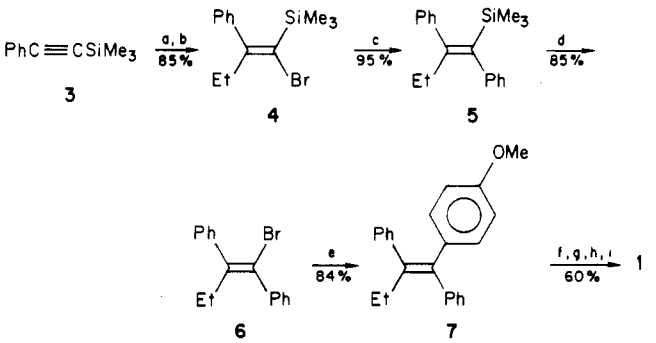
2

uses and is not only not antiestrogenic but in rats is an estrogen agonist.[5] To date, synthetic approaches to the tamoxifens have been nonstereospecific, producing mixtures of *Z* and *E* isomers which were separated by fractional crystallization techniques.[6] In this paper we report a stereospecific synthesis of (*Z*)-tamoxifen using the carbometalation of an alkynylsilane as the key step.

Results and Discussion

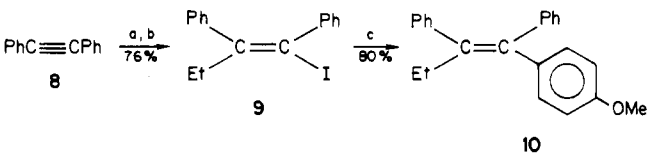
The initial step in the synthesis is based upon our recently published synthesis of 1-halo-1-(trimethylsilyl)-2,2-dialkyl olefins[7] and establishes the stereochemistry about the double bond. Thus phenyl(trimethylsilyl)-acetylene (**3**) was carbometalated with diethylaluminum chloride–titanocene dichloride to give an organometallic intermediate which was cleaved with *N*-bromosuccinimide at −78 °C. The product, **4**, by analogy to our earlier work,[7] was assinged the *E* stereochemistry. The bromine group was stereospecifically replaced by a phenyl group by palladium-catalyzed coupling[8] of **4** with phenylzinc chloride

Scheme I[a]



[a] (a) Et_2AlCl, Cp_2TiCl_2, CH_2Cl_2; (b) NBS, −78 °C; (c) PhZnCl, $Pd(PPh_3)_4$ (catalyst), THF, reflux; (d) Br_2, CH_2Cl_2, NaOMe/MeOH, −78 °C → room temperature; (e) *p*-$MeOC_6H_4ZnCl$, $Pd(PPh_3)_4$ (catalyst), THF, reflux; (f) NaSEt, DMF, reflux; (g) $ClCH_2CH_2NMe_2$·HCl, NaOEt, EtOH, reflux; (h) HCl(g), Et_2O; (i) 0.5 N NaOH.

Scheme II[a]



[a] (a) Et_2AlCl, Cp_2TiCl_2, CH_2Cl_2; (b) I_2, −78 °C; (c) *p*-$MeOC_6H_4ZnCl$, $Pd(PPh_3)_4$ (catalyst), THF, reflux.

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