were prepared and frozen at -30 °C until used. Bovine and human tissues were used in some assays (see below). Freshly dissected (or frozen) tissue was homogenized (Polytron setting 6 for 20 s) in 30 volumes of ice-cold buffer containing 50 mM Tris·HCl (pH 7.4 at 37 °C; pH 8.0 at 4 °C), 0.5 mM Na_2EDTA, and 10 mM $MgSO_4$, and centrifuged at 30000*g* for 15 min. The supernatant was discarded; the pellet was resuspended and preincubated for 15 min at 37 °C. The homogenate membranes were washed twice by centrifugation and resuspension. The final assay buffer contained 10 μM parglyine, and 0.1% ascorbate was added last to the incubation medium. Protein determinations were made by the Lowry method.

5-HT_{1A} sites were labeled with 0.1 nM [^{3}H]-8-hydroxy-2-(di-*n*-propylamino)tetralin ([^{3}H]OH-DPAT) (157 Ci/mmol; New England Nuclear) and 4 mg wet weight of rat hippocampal tissue. 8-OH-DPAT (1 μM) was used to determine nonspecific binding. The 5-HT_{1B} receptor was labeled with 2.0 nM [^{3}H]-5-HT (28.3 Ci/mmol; New England Nuclear) and 8 mg of rat striatal membrane homogenate. 5-HT (10^{-6} M) was used to define nonspecific binding, and 10^{-7} M 8-OH-DPAT and mesulergine were included to block 5-HT_{1A} and 5-HT_{1C} receptors, respectively. 5-HT_{1C} sites were labeled with 1 nM [^{3}H]-5-HT and 10 mg of rat frontal cortical tissue homogenate; 20 nM spiperone was used to mask 5-HT_2 sites. 5-HT_{1D} sites were labeled with 10 nM [^{3}H]-5-HT and 10 mg of bovine caudate homogenate; 1 μM pindolol was used to block 5-HT_{1A} and 5-HT_{1B} istes, and 100 nM mesulergine was used to block 5-HT_{1C} sites. 5-HT_{1E} sites were labeled with 2 nM [^{3}H]-5-HT and 10 mg of human cortical homogenate in the presence of 100 nM 5-carboxamidotryptamine to block any 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} sites and 100 nM mesulergine was used to block 5-HT_{1C} 5-HT_1 sites. 5-HT_2 binding studies were conducted as previously reported.[3]

Eleven concentrations of nonradioactive competing drugs were made fresh daily in assay buffer, and assays were performed in (at least) triplicate. Following incubation with membranes and radioligand at 37 °C for 30 min, samples were rapidly filtered over glass-fiber filters (Schleicher and Schuell) and were washed with 10 mL of ice-cold 50 mM Tris·HCl buffer. Individual filters were inserted into vials and equilibrated with 5 mL of scintillation fluid (Scinti-Verse, Fisher) for 6 h before counting at 50% efficiency in a Beckman 3801 counter. Results were analyzed with an updated version of the program EBDA[21] in order to determine IC_{50}, K_i, and Hill values.

Acknowledgment. This work was supported in part by US PHS Grant NS 23523.

Registry No. **2**, 304-52-9; **3**, 78263-90-8; **4**, 6260-79-3; **5**·HCl, 1453-99-2; **6**, 18658-09-8; **7**, 124224-49-3; 5-(benzyloxy)-3-(2-nitropropenyl)indole, 101731-72-0; oxalyl chloride, 79-37-8; 5-(benzyloxy)-2-methylindole, 124224-50-6; 5-methoxy-2-methylindole, 1076-74-0.

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3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 6.[1] *trans*-6-[2-(Substituted-1-naphthyl)ethyl(or ethenyl)]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-ones

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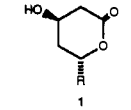
Received July 10, 1989

A variety of *trans*-6-[2-(substituted-1-naphthyl)ethyl(or ethenyl)]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-ones were prepared and, upon conversion to their 3,5-dihydroxy carboxylates, were found to have good inhibitory activity against the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-determining enzyme in cholesterogenesis. The most active compounds are 2,4,6- and 2,4,7-trichloro derivatives and would be expected to display about the same potency as the standard compactin (**1a**) upon resolution.

The enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase catalyzes the rate-determining step and point of natural regulation of cholesterogenesis. Potent inhibitors of this enzyme (e.g. **1a**) have been shown to lower cholesterol blood levels in animals and man by about 30%.[2] The results of the Lipid Research Clinics Coronary Primary Prevention Trial showed that reduction in blood cholesterol by even a modest 10% results in significantly diminished risk of coronary heart disease.[3] Thus cholesterol blood level lowering by a **1a** and similar inhibitors can be expected to significantly reduce the risk of coronary heart disease. In pursuit of this goal, we wanted to prepare wholly synthetic analogues of **1a** and **1b** without the complex stereochemistry. We began with some simple probes with modest activity.[4] Nonetheless these probes pointed the way to classes of compounds which after further ex-



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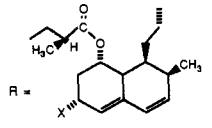
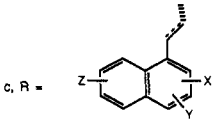
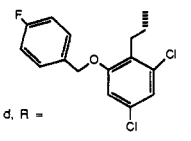
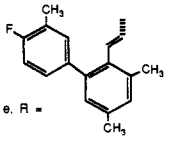


a, X = H
b, X = CH_3





d, R =



e, R =

† Rahway, NJ.

(1) Part 5: Stokker, G. E; Alberts, A. W.; Gilfillian, J. L.; Huff, J. W.; Smith, R. L. *J. Med. Chem.* **1986**, *29*, 852.
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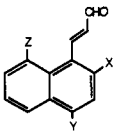
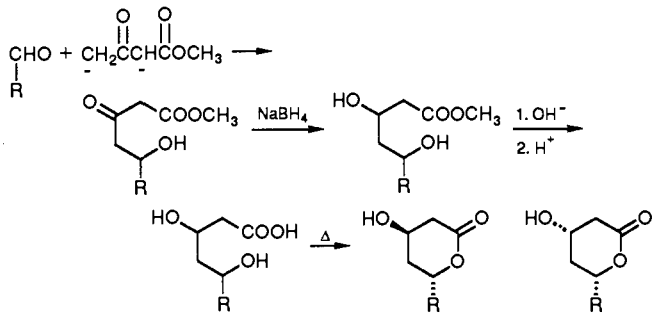
Table I. Physical Properties of 1-Naphthylpropenals

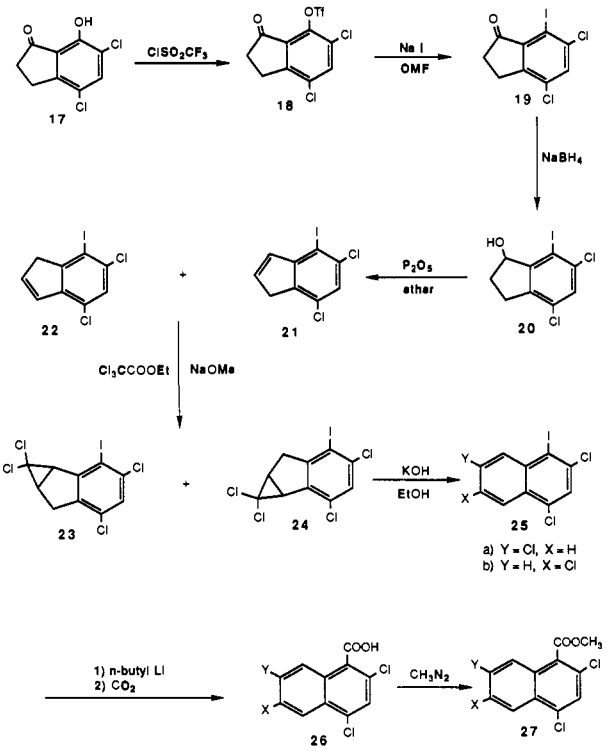


no.	X	Y	Z	recryst solvent	% yield	mp, °C	formula	anal.
14	Cl	H	H	EtOH/H_2O	44	82–84	$C_{13}H_9ClO$	C, H
15	H	Br	H	n-C_4H_9Cl	29	134–137	$C_{13}H_9BrO$	C, H
16	H	H	Br	hexane	25	96–98	$C_{13}H_9BrO$	

Scheme I



Scheme II



ploration gave benzyl ethers **1d**, which display an interesting order of activity,[5] and biphenyls **1e**, which are highly active.[6] Initial results[4] with the probe compound **1c** (x = Y = Z = H) showed sufficient activity to merit more extensive investigation. We report herein the results of further study in the **1c** series which afforded substituted naphthalene derivatives, some of which display activity similar to that of **1b**.

Chemistry

The known aldehydes 2-chloro-1-naphthaldehyde[7] and 4-bromo-1-naphthaldehyde[8] were converted to propenal intermediates **14** and **15** by the method of Baker[9] (Table I), and the lactone ring was introduced with the known chemistry[4] of Scheme I to give, respectively, 2-chloro derivative **5** and 4-bromo derivative **3**. The synthesis of 8-bromo propenal intermediate **16** (Table I) was accomplished by using the general method of Newman[10] and the lactone ring was introduced by using Scheme I technology. The double bond of **3** was hydrogenated with rhodium-on-carbon catalyst[11] to give 4.

Applying Parham methodology[12] produced the intermediate 2,4,6- and 2,4,7-trichloronaphthalene methyl ester derivatives **26** as outlined in Scheme II. Attempts to substitute the triflate of **18** with basic nucleophiles such as cyanide in DMF[13] were unsuccessful and gave only black tar. However, in a novel step the neutral nucleophile iodide ion smoothly displaced the triflate in DMF solvent. The remaining chemistry proceeded in a straightforward fashion to give esters **27**, which were separated by HPLC and assigned structures on the basis of ^{1}H NMR NOE experiments (the Experimental Section). Esters **27** were converted to the intermediate propanals **31** as outlined in Scheme III. Thus treatment of chloromethyl compounds **29** with imine carbanion **30**[14] followed by hydrolysis gave the desired aldehydes **31a** and **31b**. Introduction of the lactone ring via Scheme I technology gave final products **7** and **8**.

In the chromatographic purification of **31b**, an impurity (**33**) was isolated. Loss of the chlorine in the 2-position must have occurred during $LiAlH_4$ reduction, probably via intramolecular hydride delivery from an oxyaluminum hydride intermediate to give **32** after workup, which was then carried through the sequence undetected until the aldehyde stage. Compound **33** was then converted to **9** by using the method of Scheme I. Friedel–Crafts chemistry

(5) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 159.

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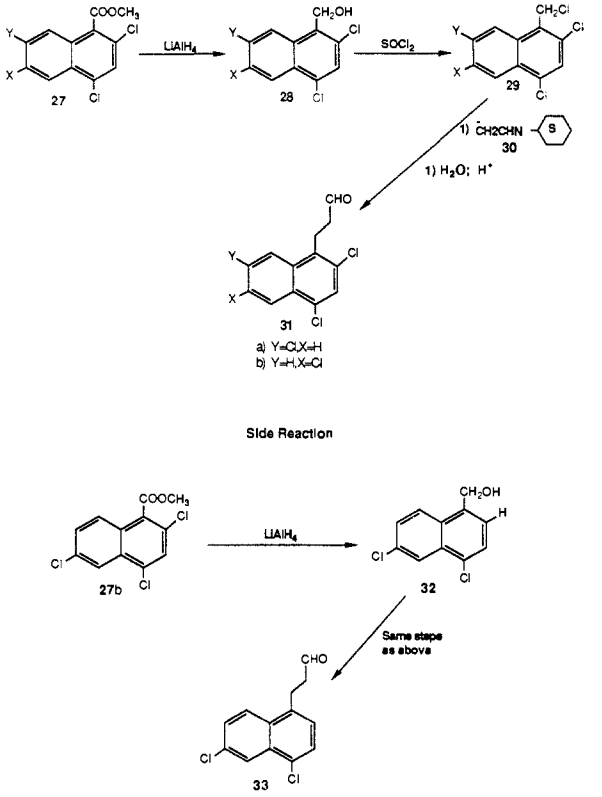
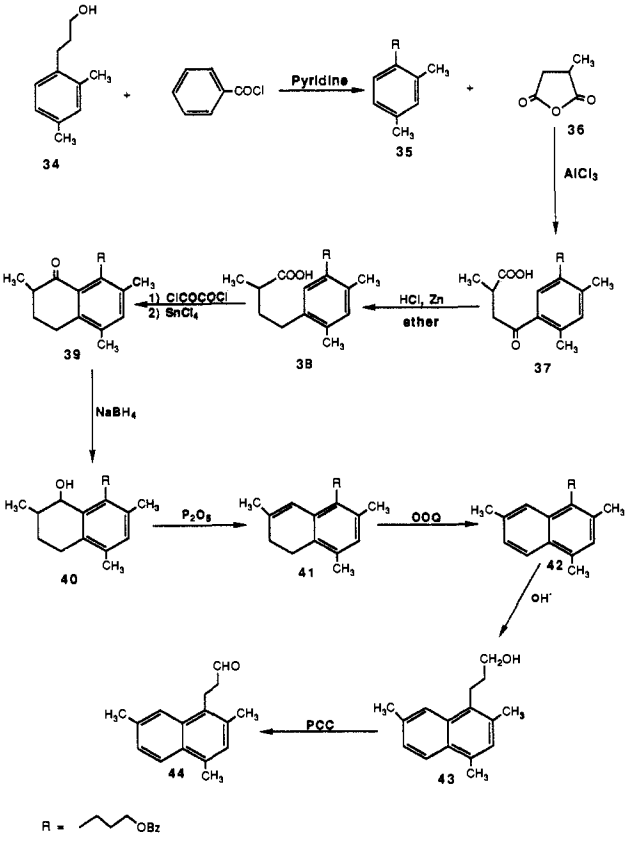
Scheme III



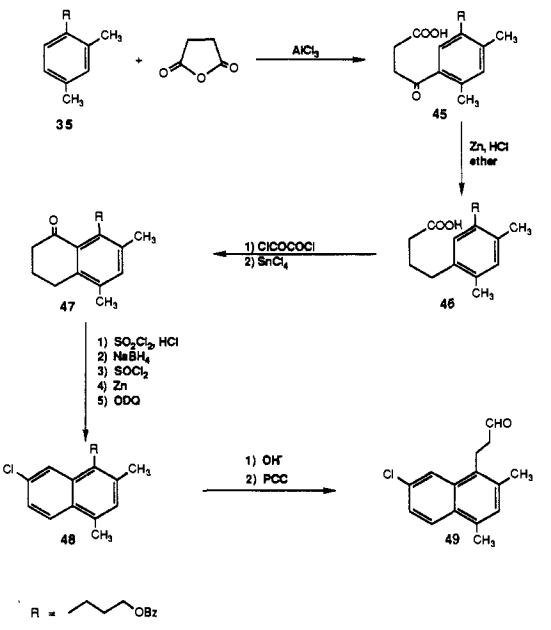
Scheme IV



was used to construct the methyl-substituted naphthalene ring via tetralones.[15] The synthesis of the needed intermediate aldehyde **44** is outlined in Scheme IV. Friedel–Crafts acylation of benzoate **35** with anhydride **36** gave **37** with high regioselectivity.[15a] The remainder of the synthesis was straightforward, giving the naphthalene aldehyde **44**, which, when carried through the lactone elaboration steps of Scheme I, gave final product **10**.

Synthesis of intermediate **49**, wherein the 7-methyl group has been replaced with chlorine, is outlined in Scheme V. The novel part of this scheme, the unambiguous introduction of the 7-chloro substituent to form **48** and **55** (Scheme VI) beginning with tetralones, has been reported[16] and briefly involved gem dichlorination α to the ketone using sulfuryl chloride, reduction of the ketone to the alcohol with $NaBH_4$, followed by conversion of the alcohol to chloride with thionyl chloride. After adjacent chlorines were removed with activated Zn to give a vinyl chloride, aromatization was completed with DDQ.

Scheme V



Scheme VI

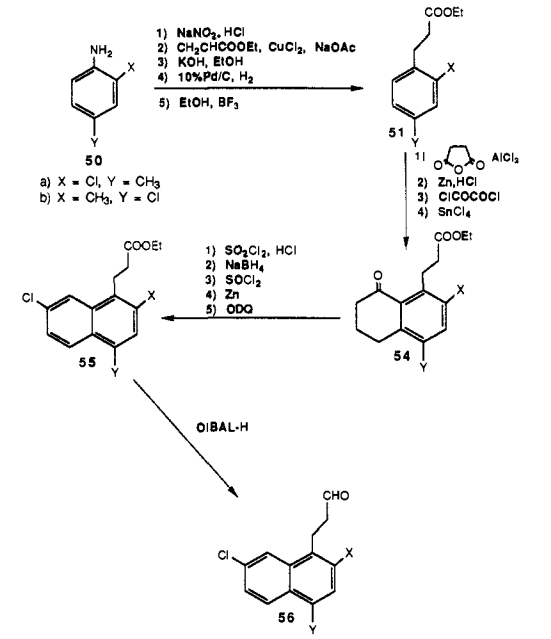


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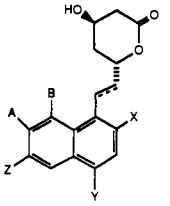
Table II. Physical Properties and in Vitro HMG-CoA Reductase Inhibitory Activities



no.	A	B	X	Y	Z	bridge	recryst solvent	mp, °C	formula	IC_{50}, μm	relative[e] potency
2	H	H	H	H	H	sat.	none	glass	$C_{17}H_{18}O_3 \cdot {}^1/_2H_2O$	81	0.043
3	H	H	H	Br	H	ene	*a*	177–179	$C_{17}H_{15}BrO_3$[c]	4	0.96
4	H	H	H	Br	H	sat.	*a*	141–143	$C_{17}H_{17}BrO_3$	23.3	0.15
5	H	H	Cl	H	H	ene	butyl chloride	88–91	$C_{17}H_{15}ClO_3$	1.51	2.3
6	H	Br	H	H	H	ene	*a*	128–129	$C_{17}H_{15}BrO_3$	4.12	0.72
7	Cl	H	Cl	Cl	H	sat.	*b*	111–115	$C_{17}H_{15}Cl_3O_3$	0.032	47
8	H	H	Cl	Cl	Cl	sat.	*b*	123–125	$C_{17}H_{15}Cl_3O_3$	0.033	46
9	H	H	H	Cl	Cl	sat.	none	glass	$C_{17}H_{16}Cl_2O_3$	7.0	0.3
10	CH_3	H	CH_3	CH_3	H	sat.	*b*	118–120	$C_{20}H_{24}O_3$	0.36	5
11	Cl	H	CH_3	CH_3	H	sat.	none	glass	$C_{19}H_{21}ClO_3$	0.2	7
12	Cl	H	CH_3	Cl	H	sat.	*a*	111–114	$C_{18}H_{18}Cl_2O_3$[d]	0.06	30
13	Cl	H	Cl	CH_3	H	sat.	*b*	126–128	$C_{18}H_{18}Cl_2O_3$	0.13	15

[a] Acetone/hexane. [b] Ether/hexane. [c] 0.05 C_6H_{14}. [d] 0.25 Et_2O. [e] Relative to compactin = 100.

We next prepared the isomeric dichloro compounds **12** and **13**. Synthesis of the intermediate aldehydes required for the straightforward elaboration of both compounds is outlined in Scheme VI. Aldehydes **56** were then transformed into target structures **12** and **13** by the chemistry shown in Scheme I.

Biological Results and Discussion

The target compounds presented in Table II as the lactones were tested as the corresponding ring-opened dihydroxy carboxylate sodium salts, the active form, in aqueous solution by using the in vitro procedure reported earlier.[4] Our investigation was limited to halogen and methyl substituents on the naphthalene ring and a brief study of the saturated or unsaturated two-carbon bridge. When comparing the bridge ene in **3** versus the saturated ethyl bridge in **4**, the activities show strong enhancement with the double bond as in the biphenyl series.[6] We reported previously[4] that the two-carbon bridge between the naphthalene ring and the lactone is optimal in a series where zero, two, and three methylene units were prepared with the naphthalene ring unsubstituted.

Halogens in the 2- and 4-positions were activity enhancing as they were in the benzyl ether[5] and the biphenyl[6] series. A halogen in the 8-position also was useful. The combination of 2,4,8-trihalo substitution is an obvious objective; however, this pattern was not readily accessible synthetically. We opted rather for the more accessible 2,4,6- and 2,4,7-trichloro compounds **7** and **8**, whose activity turned out to be outstanding and of a useful order of magnitude since they are racemates and, if resolved, would have activity comparable to compactin (**1b**). The importance of the 2-substituent was reemphasized with the nearly total loss of activity of compound **9** when compared to **8**. The synthesis of these compounds was however long and inefficient. Therefore, we next prepared all-methyl compound **10**, where the more readily executed Friedel–Crafts chemistry could be used. To our dismay it had very little activity. This result is contrary to the biphenyl series,[6] where replacement of chlorines with methyls was permissible. We concluded that at least one of the chlorines was needed. Accordingly, we replaced the 7-methyl substituent with chlorine, which gave only a small increase in activity. Clearly replacement of another chlorine was necessary, so we prepared both of the remaining chlorine substitutions at the 2- and 4-positions, leaving the chlorine in the 7-position (compounds **12** and **13**). Although most of the activity was restored, the activity of **12** and **13** is not high enough to warrant further biological evaluation.

Conclusions

A useful order of activity has been achieved in the two trichlorinated naphthalene derivatives **7** and **8**. All the permutations of a methyl substituent were not made, but those that were prepared indicate that all three chlorines are needed for a useful order of activity. The protracted and tedious chemistry of the trichlorinated compounds coupled with the inability to use Friedel–Crafts chemistry in the presence of two inactivating chlorine substituents led us to terminate this work.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) on a Varian T-60, EM-390, XL-300, or NT 360 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analysis for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of the theoretical values unless noted otherwise. All starting materials were commercially available and used as received unless so indicated.

4,6-Dichloro-7-[[(trifluoromethyl)sulfonyl]oxy]indan-1-one (18). 4,6-Dichloro-7-hydroxyindan-1-one[17] (21.71 g, 0.1 mol) was dissolved in DMF (80 mL) in a dry apparatus under nitrogen. Trifluoromethanesulfonyl chloride (21.60 g, 0.128 mol) was added with stirring, slowly, dropwise over a 20-min period with occasional cooling to keep the internal temperature below 30 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 30 min and then poured into ice–water with swirling. The green crystals were collected, washed with water, sucked dry, and then dried in a vacuum oven at 50 °C to give 32.7 g of product. mp: 96–100 °C. Recrystallization from hexanes gave 22.4 g. mp: 96–98 °C. A sublimed sample had the following. mp: 90–96 °C. Anal. ($C_{10}H_5Cl_2F_3O_4S$): C, H.

4,6-Dichloro-7-iodoindan-1-one (19). 4,6-Dichloro-7-[[(trifluoromethyl)sulfonyl]oxy]indan-1-one (56.0 g, 0.160 mol), sodium iodide (133.1 g, 0.8 mol), and DMF (320 mL) in a dry apparatus were stirred under nitrogen at a bath temperature of 130 °C for 4 days, cooled to room temperature, and poured into 1 L of ice–water. The crystals were collected, washed with water, dried

(17) Hokema, T.; Traxler, J. T. U.S. 4,322,414, 1982.

overnight in a vacuum oven at 50 °C, and then sublimed at 170–190 °C at 0.05 mm to give 38.3 g of crude product, which was recrystallized from toluene to give 31.8 g of product. mp 170–172 °C; ^{1}H NMR: δ 2.7–3.2 (4 H, m), 7.6 (1 H, s). Anal. ($C_9H_5Cl_2IO$): C, H.

4,6-Dichloro-7-iodoindan-1-ol (20). 4,6-Dichloro-7-iodoindan-1-one (14.71 g, 45 mmoles) was suspended and partially dissolved in ethanol (140 mL). Sodium borohydride (1.70 g, 45 mmol) was added and the mixture was stirred for 50 min. Aqueous sodium hydroxide 20% (w/v) (40 mL) was added and stirred for 10 min. The reaction mixture was poured into 700 mL of ice–water with vigorous stirring. The crystals were collected, washed with water, sucked dry, and dried in a vacuum oven at 50 °C overnight to give 14.08 g of the title compound, mp 95–100 °C. Recrystallization from acetonitrile gave material with the following data. mp: 99–102 °C. ^{1}H NMR: δ 2.1–3.3 (4 H, m), 5.2 (1 H, m), 7.3 (1 H, s). Anal. ($C_9H_7Cl_2IO$): C, H.

4,6-Dichloro-7-iodo-1-indene and 4,6-Dichloro-7-iodo-2-indene (21 and 22). 4,6-Dichloro-7-iodo-1-indanol (13.98 g, 42.50 mmol) was dissolved in ether (350 mL) and the solution was stirred mechanically. Phosphorus pentoxide (6.03 g 42.50 mmol) was added and the sealed reaction mixture was stirred vigorously overnight. The addition of phosphorus pentoxide (6.03 g, 42.5 mmol) and stirring overnight was repeated three times. The ether containing the product was decanted, washed with aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and filtered, and the solvent was evaporated to leave 10.76 g of a mixture of the title compounds. mp: 89–96 °C. Recrystallization from hexane gave material with the following data. mp: 95–97 °C. ^{1}H NMR: δ 3.5 (2 H, m), 6.5–6.9 (2 H, m), 7.25 (1 H, s). Anal. ($C_9H_5Cl_2I$): C, H.

1,1,3,5-Tetrachloro-1a,6a-dihydro-2-iodocycloprop[*a*]indene and 1,1,2,3-Tetrachloro-1a,6a-dihydro-5-iodocycloprop[*a*]indene (23 and 24). To a solution of a mixture of 4,6-dichloro-7-iodo-1-indene and 4,6-dichloro-7-iodo-2-indene (3.11 g, 10 mmol) and ethyl trichloroacetate (17.2 g, 12.5 mL, 90 mmol) in dry toluene (20 mL) cooled in an ice bath and stirred under nitrogen was added, in divided portions, fresh sodium methoxide (5.4 g, 100 mmol). After the addition was complete, the reaction was stirred for 2.5 h in an ice bath. When the reaction was complete, the mixture was diluted with ether and extracted with water. The ether layer was dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuo to leave 8.1 g of crude product. The product was triturated with hexanes and filtered, and the solvent was evaporated in vacuo from the hexane-soluble product. This crude product was chromatographed on silica gel (500 g) eluting with hexanes to give, after evaporation of the solvent, in vacuo, 1.4 g of the mixture of compounds as an oil. ^{1}H NMR: δ 2.2–2.55 (1 H, m), 3.15–3.6 (3 H, m), 7.2 (1 H, s).

2,4,7-Trichloro-1-iodonaphthalene and 2,4,6-Trichloro-1-iodonaphthalene (25). A mixture of 1,1,3,5-tetrachloro-1a,6a-dihydro-2-iodocycloprop[*a*]indene and 1,1,2,4-tetrachloro-1a,6a-dihydro-5-iodocycloprop[*a*]indene (4.54 g, 11.5 mmol) was refluxed in 10% (w/v) KOH in ethanol (100 mL) for 1.5 h and cooled and approximately 80% of the ethanol was evaporated in vacuo. The remainder was dissolved in ether and extracted with water, dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave 3.4 g of crude product, which was flash chromatographed on a silica gel column (60 × 150 mm) by elution with hexane to give, after evaporation of the solvent in vacuo, 2.85 g of the product mixture. mp: 45–50 °C. Ratio of the two naphthalenes is 4:5 or 5:4. ^{1}H NMR: δ 7.0–7.9 (4 H, m).

2,4,6-Trichloro-1-naphthoic Acid and 2,4,7-Trichloro-1-naphthoic Acid (Ratio 5:4 or 4:5) (26). The mixture of 2,4,7-trichloro-1-iodonaphthalene and 2,4,6-trichloro-1-iodonaphthalene (7.79 g, 21.8 mmol) was dissolved in dry ether (200 mL) and cooled under nitrogen to an internal temperature of −50 °C with stirring. Butyl lithium (17.7 mL of a 1.48 M solution in hexane, 26.2 mmol) was added dropwise over about 5 min. The reaction was stirred for 30 min at −78 °C. The −78 °C reaction mixture was poured onto powdered dry ice (excess) covered with ether. The excess CO_2 was allowed to evaporate and the ether warmed to room temperature. The ether was extracted with water once and four times with dilute aqueous $NaHCO_3$ solution. The combined aqueous extracts were acidified with concentrated HCl, the product was extracted with ether four times, dried ($MgSO_4$), and filtered, and the solvent was evaporated to leave 4.0 g of the product mixture. mp: 182–200 °C. Anal. ($C_{11}H_5Cl_3O_2$): C, H.

Methyl 2,4,6-Trichloro-1-naphthoate and Methyl 2,4,7-Trichloro-1-naphthoate (27): Preparation and Separation. The mixture of 2,4,6-trichloro-1-naphthoic acid and 2,4,7-trichloro-1-naphthoic acid (3.63 g, 13.2 mmol) was dissolved in ether and cooled to 5 °C. Diazomethane, in ether (generated from 3.40 g of *N*-nitroso-*N*-methylurea and base in 50 mL of ether at 5 °C), was added dropwise to maintain the internal temperature below 5 °C. An excess was noted by the persistence of a yellow color. The reaction mixture was stirred a few minutes and the excess diazomethane was blown off with nitrogen, and the solvent was evaporated in vacuo to leave 3.7 g of the product mixture.

The two isomers were separated by preperative HPLC (Waters 500) using 5% methylene chloride in hexane. The solvent from the first isomer to emerge from the column was evaporated in vacuo to leave 1.4 g of methyl 2,4,7-trichloro-1-naphthoate (**27a**).[18] mp: 113–115 °C. ^{1}H NMR: δ 4.09 (3 H, s), 7.25–8.25 (4 H, m). Anal. ($C_{12}H_7Cl_3O_2$): C, H.

The solvent containing the second isomer from the column was evaporated in vacuo to leave 1.1 g of methyl 2,4,6-trichloro-1-naphthoate (**27b**).[18] mp: 110–112 °C. ^{1}H NMR: δ 4.07 (3 H, s), 7.25–8.3 (4 H, m). Anal. ($C_{12}H_7Cl_3O_2$): C, H.

(2,4,7-Trichloronaphthalen-1-yl)methanol (28a). A solution of methyl 2,4,7-trichloro-1-naphthoate (1.3 g, 4.5 mmol) in ether (50 mL) was added dropwise (15 min) to a well-stirred suspension of lithium aluminum hydride (0.25 g, 6 mmol) in ether (25 mL). After stirring at room temperature for 17 h, the reaction mixture was treated with an additional 0.25 g of lithium aluminum hydride. The mixture was stirred for 3 h, cooled in an ice bath, and treated dropwise with 0.5 mL of water, 1.5 mL of 20% (w/v) of aqueous NaOH solution, and 0.5 mL of water. After filtration, the solid was extracted with ether. The combined ether solutions were dried ($MgSO_4$), filtered, and concentrated in vacuo to give 1.0 g of the product. mp: 107–112 °C. ^{1}H NMR: δ 5.23 (2 H, d), 7.55–8.28 (4 H, m).

1-(Chloromethyl)-2,4,7-trichloronaphthalene (29a). (2,4,7-Trichloronaphthalen-1-yl)methanol (1.0 g, 3.8 mmol) was added portionwise to thionyl chloride (10 mL) with cooling (ice bath). The reaction mixture was stirred at room temperature for 30 min at a reflux for 2 h and then concentrated to dryness in vacuo. The oily residue was taken up in methylene chloride and the solution was dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give 1.0 g of the product. ^{1}H NMR: δ 5.12 (2 H, s), 7.58–8.27 (4 H, m).

3-(2,4,7-Trichloronaphthalen-1-yl)propanal (31a). A solution of *n*-butyllithium in hexane (3.2 mL, 4.3 mmol) was added dropwise (3 min) to a solution of diisopropylamine (0.45 g, 4.5 mmol) in dry tetrahydrofuran (10 mL) with cooling (ice bath). After stirring under nitrogen for 15 min, ethylidenecyclohexylamine (0.55 g, 4.3 mmol) was added dropwise (5 min) at 0 °C. The mixture was stirred for 15 min and then the ice bath was replaced by a dry ice–acetone bath. A solution of 1-(chloromethyl)-2,4,7-trichloronaphthalene (1.0 g, 3.8 mmol) in tetrahydrofuran (15 mL) was added (5 min) at −75 °C. The reaction mixture was stirred at −70 °C for 30 min and at room temperature overnight (20 h) and then concentrated to dryness in vacuo. The residual oil was taken up in ether (100 mL) and 5% aqueous oxalic acid (100 mL) and the mixture was stirred at room temperature for 3.5 h. The layers were separated, and the aqueous phase was extracted (2×) with ether. The ether extracts were combined, washed with cold water and brine, and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to give a red-brown oil (1.1 g). This material was chromatographed with a 50-mm flash column containing 150 g of silica gel (230–400 mesh) eluting with 30% methylene chloride in hexane (v/v) to give 0.21 g of the product as a pale yellow solid. ^{1}H NMR: δ 2.81 (2 H, m),

(18) One of the compounds gave a 3% NOE of the proton in the 8-position when the methyl protons of the ester was irradiated. This compound was assigned structure **27a** because it has no adjacent hydrogen for relaxation of the NOE. The other compound did not show an NOE. Further, when ester **27a** is reduced to hydroxy methylene, the proton in the 8-position exhibits a 10% NOE when the methylene hydrogens are irradiated.

3.48 (2 H, m), 7.53–8.27 (4 H, m), 9.92 (1 H, b s).

3-(2,4,6-Trichloronaphthalen-1-yl)propanol (31b). With essentially the same chemistry with the other isomeric methyl 2,4,6-trichloro-1-naphthoate, there was obtained via essentially the same three steps the isomeric propanol (**31b**). ^{1}H NMR: δ 2.81 (2 H, t), 3.50 (2 H, t), 7.57 (1 H, dd), 7.63 (1 H, s), 7.93 (1 H, d), 8.28 (1 H, d), 9.91 (1 H, s). Anal. ($C_{13}H_9Cl_3O$): C, H.

3-(4,6-Dichloronaphthalen-1-yl)propanal (33). A small amount of a second product isolated by the chromatographic purification of 3-(2,4,6-trichloronaphthalen-1-yl)propanal was identified as 3-(4,6-dichloronaphthalen-1-yl)propanal by its ^{1}H NMR and by its conversion to **9**. ^{1}H NMR: δ 2.78 (2 H, t), 3.34 (2 H, t), 7.14–8.2 (5 H, m), 9.5 (1 H, s). This reduction probably took place at the reduction of the ester methyl 2,4,6-trichloro-1-naphthoate via a six-membered intramolecular hydride transfer from an intermediate oxyaluminum hydride complex and was carried through the reaction sequence.

3-(2,4-Dimethylphenyl)propyl Benzoate (35). Benzoyl chloride (21.0 g, 0.15 mol) dissolved in dry pyridine (10 mL) was added slowly dropwise (15 min) to a well-stirred solution of 3-(2,4-dimethylphenyl)propanol (21.7 g, 0.132 mol) in dry pyridine (40 mL) with cooling in an ice-water bath. The reaction was then stirred overnight and then poured into ice–water (300 mL) and the excess pyridine was removed by azeotropic evaporation of solvent in vacuo. The remainder was partitioned between ether and water. The ether layer was washed successively with water, aqueous $NaHCO_3$, and brine, and then dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuo to leave 39 g of crude product, which was distilled in vacuo to give 35.1 g of pure product. bp1.5 mm: 176–182 °C. Anal. ($C_{18}H_{20}O_2$): C, H.

4-[2,4-Dimethyl-5-[3-(benzoyloxy)propyl]phenyl]-4-oxo-2-methylbutyric Acid (37). Aluminum chloride (4.6 g, 34 mmol) was added in divided portions (5 min) to a well-stirred solution of 3-(2,4-dimethylphenyl)propyl benzoate (2.7 g, 10 mmol) and methylsuccinic anhydride (1.2 g, 10.5 mmol) in anhydrous nitroethane (15 mL), which was cooled in an ice-water bath. After the addition was complete, the ice bath was removed and the reaction stirred at ambient temperature for 2 h and then poured into ice–water (150 mL) containing 2 mL of concentrated HCl. The product was extracted (2×) with ether, and the combined ether extracts were washed with cold water and then brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave 3.8 g of crude product, which is pure enough for the next step but may be purified with silica gel flash chromatography (60 × 150 mm), eluting with methylene chloride and then a mixture of acetic acid (0.5%), acetone (4.5%), and methylene chloride (95%). After evaporation of the fractions containing the product, there remained 3.1 g of product as an oil. Anal. ($C_{23}H_{26}O_5$): C, H.

Activated Zinc Dust. Zinc dust (24 g) was stirred with 2% aqueous HCl (150 mL) for 5 min, filtered by suction, and washed with water until the washings were neutral. The zinc was then washed successively with ethanol (75 mL), acetone (150 mL), and ether and then dried in a vacuum oven at 90 °C for 15 min and then used promptly in the following reaction.

4-[2,4-Dimethyl-5-[3-(benzoyloxy)propyl]phenyl]-2-methylbutyric Acid (38). Dry gaseous HCl was bubbled vigorously into a solution of 4-[2,4-dimethyl-5-[3-(benzoyloxy)-propyl]phenyl]-4-oxo-2-methylbutyric acid (8.0 g, 20 mmol) in dry ether (360 mL) for 15 min while being cooled in an ice-water cooling bath. Activated zinc dust was added in small portions with cooling in an ice-water bath so as to keep the internal temperature below 80 °C. After the addition, the reaction was cooled with an ice–water bath and stirred for 1 h. The reaction mixture was diluted with ether and then passed onto ice-water (350 mL) containing a little HCl (2 mL) and extracted with ether (2×). The combined ether extracts were washed with water and brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated to leave 7.3 g of crude oily product, which was pure enough for the next step. A 0.2-g sample was purified by silica gel flash chromatography on a 20 × 150 mm Still column after eluting with methylene chloride and then with a mixture of 0.5% acetic acid, 4.5% acetone, and 95% methylene chloride. The fractions containing the product were combined, and the solvent was evaporated in vacuo to give 0.11 g of pure product as an oil. Anal. ($C_{23}H_{28}O_4$): C, H.

3-(5,6,7,8-Tetrahydro-2,4,7-trimethyl-8-oxonaphthalen-1-yl)propyl Benzoate (39). A solution of 4-[2,4-dimethyl-5-[3-(benzoyloxy)propyl]phenyl]-2-methylbutyric acid (7.4 g, 20 mmol) in methylene chloride (20 mL) was added dropwise in 10 min to oxalyl chloride (20 mL) with stirring and cooling in an ice-water bath. After the addition, the reaction was stirred at room temperature for 30 min and then warmed slowly to a bath temperature of 65 °C when the reaction refluxed. The refluxing was continued with stirring for 2 h. The reaction was then cooled, and the excess oxalyl chloride and solvent were evaporated in vacuo to leave 4-[2,4-dimethyl-5-[3-(benzoyloxy)propyl]phenyl]-2-methylbutyryl chloride as an oil which was dissolved in dry methylene chloride (20 mL) and cooled in an ice-water bath. To this was added a solution of stannic chloride (20 mL) in dry methylene chloride (20 mL) at a rapid drip (10 min). The reaction was stirred at room temperature for 30 min and poured into ice–water (300 mL), containing concentrated HCl (20 mL). The mixture was extracted with ether (3×). The combined ether extracts were washed successively with water twice, aqueous sodium bicarbonate, water, and brine, dried ($MgSO_4$), and filtered and the solvent was evaporated to leave 7.2 g of crude product, which was purified by silica gel flash chromatography using an 80 × 160 mm Still column eluting with methylene chloride for 35 × 125 mL fractions and then 2% acetone in methylene chloride for 20 × 125 mL fractions. The fractions containing the product were combined, and the solvent was evaporated in vacuo to leave 3.3 g of oil product. ^{1}H NMR: δ 1.22 (3 H, d), 1.82 (1 H, m), 2.00 (1 H, m) 2.1–2.3 (2 H, m), 2.23 (3 H, s), 2.34 (3 H, s), 2.66 (1 H, m), 2.80 (1 H, m), 2.90 (1 H, m), 3.04 (2 H, t), 4.47 (2 H, t), 7.14 (1 H, s), 7.45 (2 H, t), 7.56 (1 H, t), 8.10 (2 H, d). Anal. ($C_{23}H_{26}O_3$): C, H.

***cis*- and *trans*-3-(5,6,7,8-Tetrahydro-8-hydroxy-2,4,7-trimethylnaphthalenyl)propyl Benzoate (40).** Sodium borohydride (0.50 g, 13 mmol) was added in divided portions to a stirred solution of 3-(5,6,7,8-tetrahydro-2,4,7-trimethyl-8-oxonaphthalen-1-yl)propyl benzoate (2.65 g, 7.5 mmol) in ethanol (40 mL) and then stirred at room temperature for 7 h (reaction complete by TLC; 1% acetone in methylene chloride–silica gel). The clear reaction was poured into ice water, acidified with dilute HCl, and extracted with ether (3×). The combined ether extracts were washed successively with cold water and brine, dried ($MgSO_4$), filtered, and the solvent was evaporated in vacuo to leave 2.7 g of the product.

3-(5,6-Dihydro-2,4,7-trimethylnaphthalen-1-yl)propyl Benzoate (41). *cis*- and *trans*-3-(5,6,7,8-tetrahydro-8-hydroxy-2,4,7-trimethylnaphthalen-1-yl)propyl benzoate (2.7 g, 7.7 mmol) were dissolved in dry ether (200 mL), to this was added powdered phosphorus pentoxide (5 g), and the sealed reaction mixture was stirred overnight. The addition of phosphorus pentoxide and stirring overnight was repeated once. When TLC (1% acetone in methylene chloride/silica gel) showed the reaction to be complete. The ether was decanted and the residue was washed with ether by decantation. The phosphorus residue was treated with ice–water and extracted with ether. The combined ether decantations and washings were washed successively with water, aqueous sodium bicarbonate, and brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated to leave 2.8 g of crude product. This product was purified by flash chromatography on a 50 × 160 mm Still column eluting with 50% hexane in methylene chloride. The fractions containing the product were combined, and the solvent was evaporated in vacuo to give 1.6 g of oil product. ^{1}H NMR: δ 1.66–2.2 (2 H, m), 1.9 (3 H, s), 2.2 (3 H, s), 2.25 (3 H, s), 2.6–3.0 (6 H, m), 4.2 (2 H, s), 6.45 (1 H, s), 6.8 (1 (H, s), 7.2–7.6 (3 H, m), 7.9–8.1 (2 H, m).

3-(2,4,7-Trimethylnaphthalen-1-yl)propyl Benzoate (42). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ); 0.95 g, 42 mmol) was added to a solution of 3-(5,6-dihydro-2,4,7-trimethylnaphthalen-1-yl)propyl benzoate (1.25 g, 37 mmol) in toluene (60 mL) and stirred at room temperature for 1 h. The reaction mixture was filtered and the solvent was evaporated in vacuo to leave crude product. This product was purified by flash chromatography on a 50 × 150 mm Still silica column eluting with 50% hexane in methylene chloride. The fractions containing the product were combined, and the solvent was evaporated in vacuo to leave 0.78 g of oil product. ^{1}H NMR: δ 2.12 (2 H, m), 2.47 (3 H, s), 2.49 (3 H, s), 2.62 (3 H, s), 3.22 (2 H, t), 4.52 (2 H, 5), 7.19

(1 H, s), 7.29 (1 H, d), 7.48 (2 H, t), 7.59 (1 H, t), 7.83 (1 H, s), 7.87 (1 H, d), 8.12 (2 H, d). Anal. ($C_{23}H_{24}O_2$): C, H.

3-(2,4,7-Trimethylnaphthalen-1-yl)propanol (43). A solution of 3-(2,4,7-trimethylnaphthalen-1-yl)propyl benzoate (0.75 g, 2.3 mmol) was added to a solution of potassium hydroxide (0.5 g, 7 mmol) in ethanol (50 mL) and stirred at room temperature for 4 h. Most of the ethanol was evaporated in vacuo and the residue was partitioned between ether and water. The ether was washed with water twice, dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave 0.53 g of product.

3-(2,4,7-Trimethylnaphthalen-1-yl)propanol (44). 3-(2,4,7-Trimethylnaphthalen-1-yl)propanol (0.68 g, 3 mmol) was added to a suspension of pyridinium chlorochromate (1.28 g, 6 mmol) in methylene chloride (20 mL). The reaction mixture was stirred at room temperature for 2 h and then diluted with ether (10 mL) and the solvent was decanted. The black solids were washed with ether by decantation twice. The combined organic extracts were filtered through a pad of Florisil, and the solvent was evaporated in acid to leave 0.53 g of product. Recrystallization from petroleum ether gave a white crystalline solid. mp: 79–83 °C. ^{1}H NMR: δ 2.44 (3 H, s), 2.54 (3 H, s), 2.62 (3 H, s), 2.77 (2 H, t), 3.36 (2 H, t), 7.09 (1 H, s), 7.31 (1 H, d), 7.69 (1 H, s), 7.88 (1 H, d), 9.93 (1 H, t). Anal. ($C_{16}H_{18}O$): C, H.

3-(5,6,7,8-Tetrahydro-2,4-dimethyl-8-oxonaphthalen-1-yl)propyl Benzoate. Following the experimental method of the 2,4,7-trimethyl analogue but substituting succinic anhydride for 3-methyl succinic anhydride, there was obtained in succession the following.

4-[2,4-Dimethyl-5-[3-(benzoyloxy)propyl]phenyl]-4-oxobutyric acid (45) as an oil (3.68 g, 78%). Anal. ($C_{22}H_{25}O_5$): C, H.

4-[2,4-Dimethyl-5-[3-(benzoyloxy)propyl]phenyl]butyric Acid (46).

3-(5,6,7,8-Tetrahydro-2,4-dimethyl-8-oxonaphthalen-1-yl)propyl Benzoate (47). TLC: R_f = 0.33, 1% acetone/CH_3Cl_2. ^{1}H NMR: δ 1.75–2.42 (4 H, m), 2.42 (3 H, s), 2.50 (3 H, s), 2.50–2.95 (4 H, m), 2.95–3.32 (2 H, m), 4.72 (2 H, t), 7.15 (1 H, s), 7.3–7.55 (3 H, m), 7.92–8.15 (2 H, m).

7-Chloro-2,4-dimethyl-1-(3-hydroxypropyl)naphthalene. 1-[3-(Benzoyloxy)propyl]-7-chloro-2,4-dimethylnaphthalene (48) (2.60 g, 7.37 mmol) was suspended in ethanol (30 mL) and potassium hydroxide (1.65 g, 29.5 mmol) added and stirred at room temperature for 2 h then at 60–65 °C bath temperature for 1 h. The reaction mixture was cooled in an ice bath, filtered from sodium benzoate, and washed thoroughly with ethanol. The combined filtrates were dissolved in ether and extracted with water. The water was extracted with ether three times. The combined ether extracts were washed with water three times and then with brine, dried ($MgSO_4$) and filtered, and the solvent was evaporated to leave 1.80 g (98%) of the product. A sublimed sample [100 °C bath temp (0.1 mm)] had mp 104–105 °C. Exact mass calcd for $C_{15}H_{17}ClO$: 248.0968. Found: 248.0968. ^{1}H NMR: δ 1.60–2.20 (4 H, m), 2.44 (3 H, s), 2.56 (3 H, s), 3.05 (2 H, q), 3.74 (2 H, t), 7.0–7.95 (4 H, m).

3-(7-Chloro-2,4-dimethylnaphthalen-1-yl)propanal (49). Pyridinium chlorochromate (3.12 g, 14.47 mmol) and powdered 3-Å molecular sieves (3.6 g) were suspended in methylene chloride (25 mL), and 7-chloro-2,4-dimethyl-1-(3-hydroxypropyl)-naphthalene (1.70 g, 6.83 mmol) dissolved in methylene chloride (25 mL) was added all at once and stirred for 2 h. The reaction mixture was worked up by diluting with ether (50 mL) and filtering through a silica gel pad. The pad was washed with ether and the solvent was evaporated in vacuo to give 1.24 g (73%) of product. Exact mass calcd for $C_{15}H_{15}ClO$: 246.0811. found: 246.0813. ^{1}H NMR: δ 2.3–2.95 (2 H, m), 2.40 (3 H, s), 2.55 (3 H, s), 3.25 (2 H, t), 7.02–8.0 (4 H, m). TLC: R_f = 0.36 (50% CH_2Cl_2–hexane/silica gel).

Ethyl 3-(4-Chloro-2-methylphenyl)propionate (51b). Boron trifluoride etherate (1.5 mL, 0.012 mol) was added dropwise to a solution of 3-(4-chloro-2-methylphenyl)propionic acid (1.99 g, 0.01 mol) in absolute ethanol (14 mL). The reaction mixture was heated at reflux for 6.5 h, cooled, and concentrated in vacuo to remove the solvent, and the residual oil was taken up in ether. The ether solution was washed with aqueous Na_2CO_3 and cold water, dried, and evaporated to give an orange oil, which was distilled at about 1.5 mm to give the product as an oil (1.5 g, 66%). bp: 126–131 °C. Anal. ($C_{12}H_{15}ClO_2$): C, H.

4-[2′-Chloro-4′-methyl-5′-[2-(ethoxycarbonyl)ethyl]-phenyl]-4-oxobutyric Acid (52b). Aluminum chloride (5.87 g, 0.044 mol) was added portionwise (5 min) to a mixture of succinic anhydride (1.1 g, 0.011 mol) and ethyl 3-(4-chloro-2-methylphenyl)propionate (2.27 g, 0.01 mol) in CH_2Cl_2 (20 mL) with cooling (ice bath). The reaction mixture was stirred at room temperature for 24 h, poured into ice and 10 mL of concentrated HCl, and extracted with ether. The ether solution was dried and evaporated to give a yellow brown oil, which was purified by flash column chromatography (silica gel and 2% HOAc–10% acetone–90% CH_2Cl_2) to give the product as a yellow oil (3.0 g, 92% yield). Anal. ($C_{16}H_{19}ClO_5$): C, H.

4-[2′-Chloro-4′-methyl-5′-[2-(ethoxycarbonyl)ethyl]-phenyl]butyric Acid (53b). Gaseous HCl was bubbled into a well-stirred solution of 4-[2′-chloro-4′-methyl-5′-[(ethoxycarbonyl)ethyl]phenyl]-4-oxobutyric acid (3.27 g, 0.01 mol) in acetic anhydride (60 mL) for 20 min with cooling (ice–acetone bath). Activated zinc dust (13.11 g 6.2 mol) was added portionwise (15 min) to keep the temperature below 0 °C. The reaction mixture was stirred at about 0 °C for 7 h, filtered (glass wool) into ice and water and extracted with ether. The ether solution was dried and evaporated to give a brown oil, which was purified by flash column chromatography (silica gel and 0.5% HOAc–4.5% acetone–95% CH_2Cl_2) to yield the product as a viscous yellow oil (2.17 g, 69%).

Ethyl 3-(4-Chloro-2-methyl-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)propanoate (54b). Oxalyl chloride (23.5 mL) was added dropwise to a well-stirred solution of 4-[2′-chloro-4′-methyl-5′-[(ethoxycarbonyl)ethyl]phenyl]butyric acid (10.38 g, 0.033 mol) in toluene (50 mL). The reaction mixture was stirred at room temperature for 18 h, heated at reflux for 4 h, cooled, and concentrated to dryness, and the residual oil was taken up in CH_2Cl_2 (50 mL). After addition of stannic chloride (31.5 mL) with cooling (ice bath), the reaction mixture was stirred at room temperature for 5 days and then poured into ice and concentrated HCl (20 mL) and extracted with ether. The ether solution was dried and evaporated to give a viscous brown oil, which after silica gel chromatography eluting with 15% ethyl acetate in hexane gave the product as a gum. Exact mass calcd for $C_{16}H_{19}ClO_3$: 284.1021. Found: 294.1019. ^{1}H NMR: δ 1.27 (3 H, t, CH_2CH_3), 2.10 (2 H, p, CH_2), 2.34 (3 H, s, $ArCH_3$), 2.57 (2 H, t, CH_2), 2.65 (2 H, t, CH_2), 2.99 (2 H, t, CH_2), 3.21 (2 H, t, CH_2), 4.16 (2 H, q, CH_2CH_3), 7.36 (1 H, s, Ar).

3-(4,7-Dichloro-2-methylnaphthalen-1-yl)propanal (56b). Ethyl 3-(4,7-dichloro-2-methylnaphthalen-1-yl)propanoate (1.583 g, 5.087 mmol) was dissolved in dry toluene (25 mL) under nitrogen with syringe cap attached to flask. The solution was cooled to −78 °C in dry ice–acetone bath and diisobutylaluminum hydride (3.62 mL of a 1.5 M solution in toluene, 5.443 mmol) was added dropwise slowly by syringe. Stirring was continued at −78 °C for 1 h. Then while still at −78 °C, the reaction was poured quickly into an aqueous NH_4Cl solution with stirring. This mixture was extracted two times with ether. The combined ether extracts were extracted successively with NH_4Cl solution, water, and brine, and then dried ($MgSO_4$), and filtered, and the solvent was evaporated to leave a solid. This solid was triturated with a little ether in hexane to give 0.701 g of pure solid product (mp: 104–106 °C). The solvent was stripped from the mother liquor to give 0.681 g of impure product. This impure product was flash chromatographed on a 20 × 200 mm silical column eluting with 70% CH_2Cl_2 in hexane to give 0.45 g of pure solid product. mp: 103–105 °C. Combining the two samples of pure solid product gave 1.15 g of pure product (mp: 104–106 °C) after drying. ^{1}H NMR: δ 2.47 (3 H, s, CH_3), 2.76 (2 H, t, CH_2), 3.28 (2 H, t, CH_2), 7.42 (1 H, s, Ar), 7.49 (1 H, dd, Ar), 7.90 (1 H, d, Ar), 8.22 (1 H, d, Ar), 9.92 (1 H, s, *CHO*). Anal. ($C_{14}H_{12}Cl_2O$) C, H.

With the above experimental procedures but substituting 3-(2-chloro-4-methylphenyl)propionic acid for 3-(4-chloro-2-methylphenyl)propionic acid there was obtained in succession the following.

Ethyl 3-(2-Chloro-4-methylphenyl)propanoate (51a). Bp: 104–107 °C. Anal. ($C_{12}H_{15}ClO_2$): C, H.

4-[4-Chloro-2-methyl-5-[2-(ethoxycarbonyl)ethyl]-phenyl]-4-oxobutyric Acid (52a). Mp: 72–74 °C. Anal. ($C_{16}H_{19}ClO_5$): C, H.

4-[4-Chloro-2-methyl-5-[2-(ethoxycarbonyl)ethyl]-phenyl]butyric Acid (53a). Mp: 50–52 °C. Anal. ($C_{16}H_{21}ClO_4$): C, H.

Ethyl 3-(2-Chloro-4-methyl-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl) (54a). Mp: 63–65 °C. Anal. ($C_{16}H_{19}ClO_3$): C, H.

3-(2,7-Dichloro-4-methylnaphthalen-1-yl)propanal (56a). mp: 103–105 °C. ^1H NMR: δ 2.66 (3 H, s), 2.82 (2 H, t), 3.49 (2 H, t), 7.34 (1 H, s), 7.52 (1 H, d), 7.95 (2 H, m), 9.95 (1 H, s). Anal. ($C_{14}H_{12}Cl_2O$): C, H.

Registry No. 2, 124243-86-3; 2·Na, 124244-18-4; 3, 124243-87-4; 3·Na, 124244-19-5; 4, 124243-88-5; 4·Na, 124244-20-8; 5, 124243-89-6; 5·Na, 124244-21-9; 6, 124243-90-9; 6·Na, 124244-22-0; 7, 124243-91-0; 7·Na, 124244-23-1; 8, 124243-92-1; 8·Na, 124244-24-2; 9, 124243-93-2; 9·Na, 124244-25-3; 10, 124243-94-3; 10·Na, 124244-26-4; 11, 124243-95-4; 11·Na, 124244-27-5; 12, 108579-26-6; 12·Na, 124244-28-6; 13, 108579-36-8; 13·Na, 124244-29-7; 14, 124243-96-5; 15, 124243-97-6; 16, 124243-98-7; 17, 81945-11-1; 18, 108578-92-3; 19, 108578-93-4; 20, 10578-94-5; 21, 108578-95-6; 22, 108578-96-7; 23, 108578-97-8; 24, 108578-98-9; 25a, 108578-99-0; 25b, 108579-00-6; 26a, 108579-02-8; 26b, 108579-01-7; 27a, 108579-04-0; 27b, 108579-03-9; 28a, 108579-05-1; 28b, 124244-13-9; 29a, 108579-06-2; 29b, 124244-14-0; 31a, 108579-07-3; 31b, 108579-11-9; 33, 124243-99-8; 34, 27650-80-2; 35, 124244-00-4; 37, 124244-01-5; 38, 124244-02-6; 39, 124244-03-7; *cis*-40, 124244-04-8; *trans*-40, 124244-17-3; 41, 124244-05-9; 42, 124244-06-0; 43, 124244-07-1; 44, 124244-08-2; 45, 124266-46-2; 46, 124244-09-3; 47, 124244-10-6; 48, 124244-11-7; 49, 124244-12-8; 50a, 615-65-6; 50b, 95-69-2; 51a, 108579-27-7; 51b, 108579-13-1; 52a, 108579-28-8; 52b, 108579-14-2; 53a, 108579-29-9; 53b, 108579-15-3; 54a, 108579-30-2; 54b, 108579-16-4; 55a, 108579-34-6; 55b, 108579-22-2; 56a, 108579-35-7; 56b, 108579-23-3; Cl_3CCO_2Et, 515-84-4; $H_2^-CCOC^-HCO_2Me$, 30568-00-4; 3-hydroxy-3-methylglutaryl-coenzyme A, 1553-55-5; *N*-ethylidenecyclohexylamine, 1193-93-7; methylsuccinic anhydride, 4100-80-5; succinic anhydride, 108-30-5; 7-chloro-2,4-dimethyl-1-(3-hydroxypropyl)naphthalene, 124244-15-1; 3-(4-chloro-2-methylphenyl)propionic acid, 879-75-4; 3-(2-chloro-4-methylphenyl)propionic acid, 124244-16-2.

Lipophilic 1,3-Xylyl-21-crown-6 Macrocyclic Polyether 2-Carboxylic Acids as Biological Mimics of the Ionophore Antibiotics

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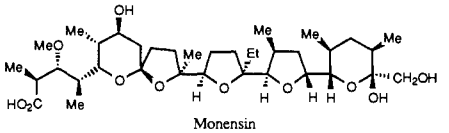
Twelve lipophilic 1,3-xylyl-21-crown-6 macrocyclic polyether 2-carboxylic acids (**9a–9l**), two lariat ether 1,3-xylyl-21-crown-6 macrocyclic polyether 2-carboxylic acids (**21** and **22**), and two 1,3-xylyl-28-crown-8 macrocyclic polyether 2-carboxylic acids (**10a** and **10b**) were synthesized and tested for in vitro antibacterial activity, in vitro stimulation of rumen propionic acid production, and in vivo anticoccidial activity in chickens. These are biological screens relevant to animal health areas where the ionophore antibiotics such as monensin have found application. While the parent structure **1** without lipophilic substituents was biologically inactive, the lipophilic macrocycles were active in the two in vitro tests but not against chicken coccidiosis. One compound (**9f**) was tested in cattle and was found to increase levels of propionic acid in the rumen fermentation. This effect is considered an important factor for increasing the efficiency of feed utilization in cattle exhibited by the ionophore antibiotic monensin. The alkali ion salts of these lipophilic macrocyclic polyether carboxylic acids are very soluble in organic solvents and insoluble in water. These compounds are proposed to act as ion-transport agents and functional mimics of the ionophore antibiotics in the biological systems described above.

The ionophore antibiotics with their fascinating array of complex structures have provided a continuing challenge to organic chemists.[1] These compounds exhibit unique activity in many biological systems via a mechanism of action which is deceptively simple: the exchange of alkali ions for protons across biological membranes.[2] Synthetic molecules which try to mimic the physical properties of the natural antibiotics have been described,[3] but only marginal success was achieved in demonstrating biological activity and no in vivo activity in either animal health area where the ionophores have made a major impact, coccidiosis control in chickens or cattle performance enhancement, has been reported. In this paper, we describe our efforts in the synthesis of polyether mimics of natural ionophores with in vivo activity in cattle and in vitro antibacterial activity.

In 1967, monensin was the first polyether antibiotic to have its structure[4] and potent biological activities,[5] such as inhibition of alkali metal cation transport in mitochondria and broad-spectrum anticoccidial activity, disclosed. It was approved for commercial use as a poultry anticoccidial in 1971 and as a cattle performance enhancer in 1975. The structure of the silver salt of monensin,[4] which is typical for the entire class, has a lipophilic exterior and a hydrophilic central cavity lined with oxygen atoms which serve as ligands for encapsulated alkali ions; the molecule as a whole is therefore neutral and lipophilic. When the carboxylate is protonated, at an interface, either biological or in solvent, the complexation of the ion, while still possible in dry, organic solvents, is weaker by several orders of magnitude[6] and the alkali ion is readily given up to the acidic aqueous layer. It is this large difference in complexation constant for alkali ions between the carboxylic acid and the carboxylate forms of the ionophore



Monensin

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0022-2623/90/1833-0765$02.50/0