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Studies on Hypolipidemic Agents. I.[1] Synthesis of 1,3-Dioxolanes and 1,3-Dioxanes

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2-Aryl-substituted 3a,4,5,9b-tetrahydronaphtho[1,2-*d*]-1,3-dioxolanes (**4**), 5-phenyl- (**6**), 5-(1,2,3,4-tetrahydro-2-naphthyl)- (**7**) and 5-(2-naphthyl)-1,3-dioxanes (**8**) and 3-aryl-substituted 1*H*-naphtho[2,1-*d*][1,3]dioxins (**5**) were synthesized. Among them, the 1,3-dioxanes (**6**—**8**) were each obtained as a mixture of the *trans* and *cis* isomers. Two stereoisomers of the 2-(3-pyridyl)-substituted derivatives (**6c** and **7c**) and the *trans* isomers of the other 1,3-dioxanes (**6**—**8**) were isolated and their stereostructures are discussed.

Most of the *trans* isomers of **6**—**8** showed potent hypolipidemic activity, while the *cis* isomers were inactive. The most active compound was the *trans* isomer of **7c**.

Keywords——3a,4,5,9b-tetrahydronaphtho[1,2-*d*]-1,3-dioxolane; 5-phenyl-1,3-dioxane; 5-(1,2,3,4-tetrahydro-2-naphthyl)-1,3-dioxane; 5-(2-naphthyl)-1,3-dioxane; 1*H*-naphtho[2,1-*d*][1,3]dioxin; stereoisomer; hypolipidemic activity; structure-activity relationship

The estrone (**1**) has a well-known hypocholesterolemic activity in rats. In an attempt to find new hypolipidemic agents, we have investigated some derivatives of 3-methoxyestra-1,3,5(10)-triene-$16\beta,17\beta$-diol (**2**), and found that 3-methoxyestra-1,3,5(10)-trieno[$16\beta,17\beta$-*d*]-

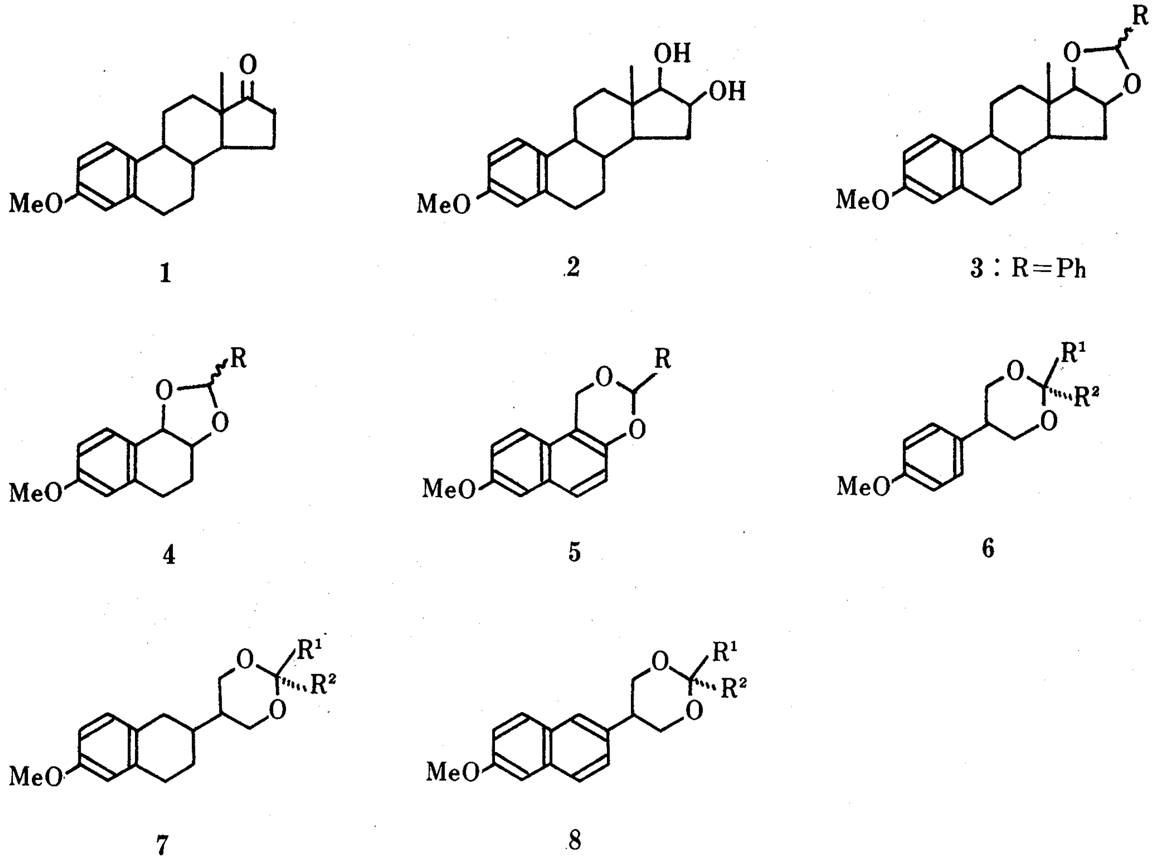


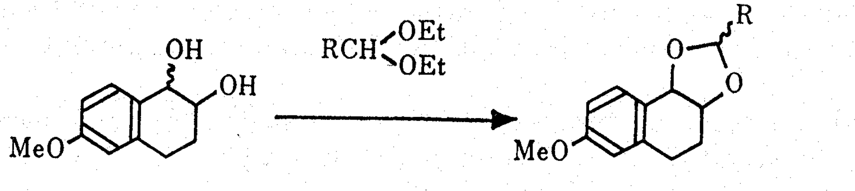
Chart 1

2′-phenyl-1′,3′-dioxolane (3) and its analogs having various aryl groups at C_2' exhibited potent hypocholesterolemic activity.[2] However, these compounds were of limited practical use because their estrogenic activity produced an unpleasant side-effect.[2] Thus, we prepared nonsteroidal dioxolane (or dioxane) derivatives as shown in Chart 1, based on the assumption that the aromatic ring and 1,3-dioxolane ring in **3** might be required for hypolipidemic activity whereas the steroidal structure might be more important for the estrogenic property. The present paper deals with the preparation of **4**—**8** and presents the results of preliminary biological studies.

2-Substituted 7-Methoxy-3a,4,5,9b-tetrahydronaphtho[1,2-*d*]-1,3-dioxolanes (4)

Heating of 1,2-dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (**9**),[3] prepared according to Nagata's procedure,[4] with various aromatic acetals gave the corresponding 1,3-dioxolanes (**4a**—**c**).

The assigned structures of **4a**—**c** were supported by their infrared (IR) and nuclear magnetic resonance (NMR) spectra. Though the stereochemistry of the aryl groups at C_2 in **4a**—**c** remained to be determined, the fact that the signal of the methine proton (C_2–H) in their NMR spectra was observed only as a singlet suggested that these compounds (**4a**—**c**) each consisted of a single stereoisomer at C_2. According to the report of Eliel *et al.* on the NMR spectra of 2,4,5-trisubstituted 1,3-dioxolanes, stereoisomers at C_2 showed different chemical shifts of the signal due to the methine proton (C_2–H).[5]



9

4a—**c**
4a : R=Ph
4b : R=4-MeO-Ph
4c : R=3-pyridyl

Chart 2

3-Substituted 8-Methoxy-1*H*-naphtho[2,1-*d*][1,3]dioxins (5)

The synthesis of **5** was carried out as shown in Chart 3. Treatment of 6-methoxy-2-naphthol (**10**) with $Zn(CN)_2$,[6] followed by acidic hydrolysis of the resulting imino compound afforded the aldehyde (**11**), which was reduced to the diol (**12**) with $NaBH_4$. Cyclization of **12** with benzal chloride in the presence of *tert*-BuOK gave the desired 1,3-dioxin (**5a**) in very low yield. In an attempt to cyclize **12** by heating it with anisaldehyde diethylacetal, the main product was not the desired 1,3-dioxin (**5b**), but the compound **13**. Its structure was confirmed by spectral analysis to be 1′,2′-dihydrospiro[naphthalene-1(2*H*), 3′-[3*H*]naphtho[2,1-*b*]pyran]-2-one, which has been reported by Catterall.[7]

2-Substituted 5-(4-Methoxyphenyl)-1,3-dioxanes (6)

Treatment of ethyl 4-methoxyphenylacetate (**14**) with paraformaldehyde and Triton B[8] to form the monoester (**15**), followed by reduction with $LiAlH_4$ gave the diol (**16**). Reaction of **16** with various aromatic aldehydes in the presence of a catalytic amount of *p*-toluenesulfonic acid in benzene by means of a Dean–Stark apparatus afforded the corresponding 1,3-dioxanes (**6a**—**e**).

NMR spectra of the crude products showed that the 2-phenyl-1,3-dioxanes (**6a**, **b**) were present only as the *trans* isomers, while the 2-pyridyl-1,3-dioxanes (**6c**—**e**) were mixtures of stereoisomers, composed mostly of the *trans* isomers. In the case of **6c**, the *trans* and *cis* isomers were isolated in 85.5 and 2.5% yields, respectively.

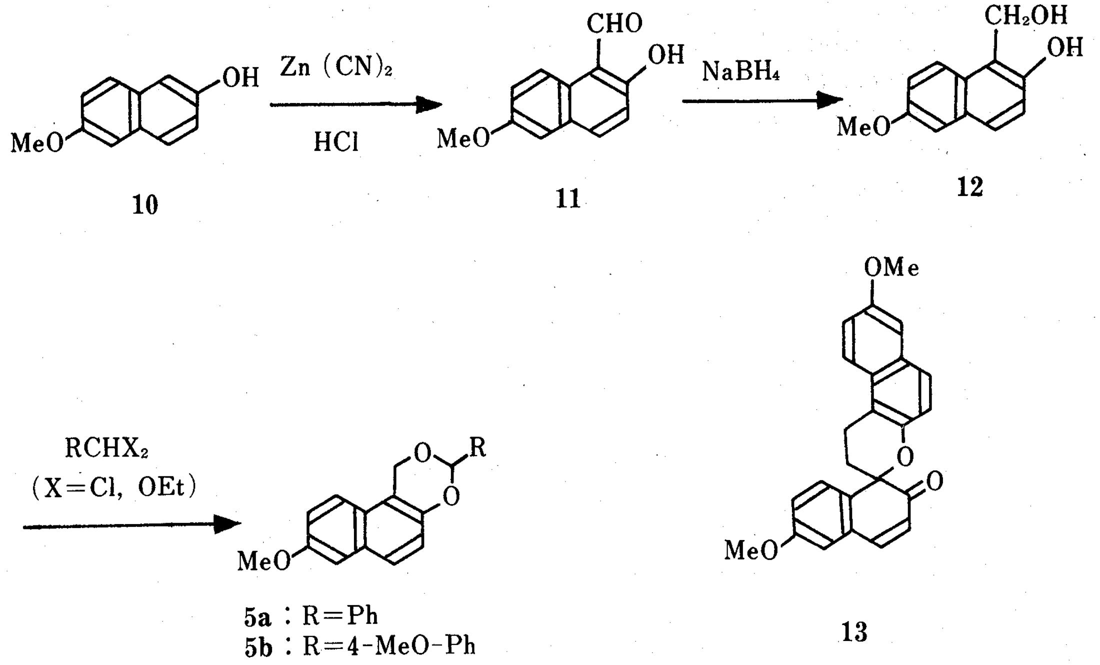


Chart 3

Treatment of the *trans* isomers of **6c**, **d** with ethyl iodide gave the pyridinium salts, which were then led to the corresponding piperidine derivatives (**6f**, **g**) by catalytic reduction with PtO_2.

In the NMR spectrum of *trans*-5-(4-methoxyphenyl)-2-(3-pyridyl)-1,3-dioxane (**6ct**), the vicinal *J*-values between the methine proton (C_5–H) and the axial and equatorial protons of two equivalent methylene groups (C_4–H_2 and C_6–H_2) were 11.4 and 5.4 Hz, respectively. This result showed that C_5–H of **6ct** is axially oriented. On the other hand, the NMR spectrum of the *cis* isomer (**6cc**) showed that C_5–H is equatorially oriented. A similar discussion of the stereochemistry of other 1,3-dioxane derivatives has been made by Bauman.⁹⁾

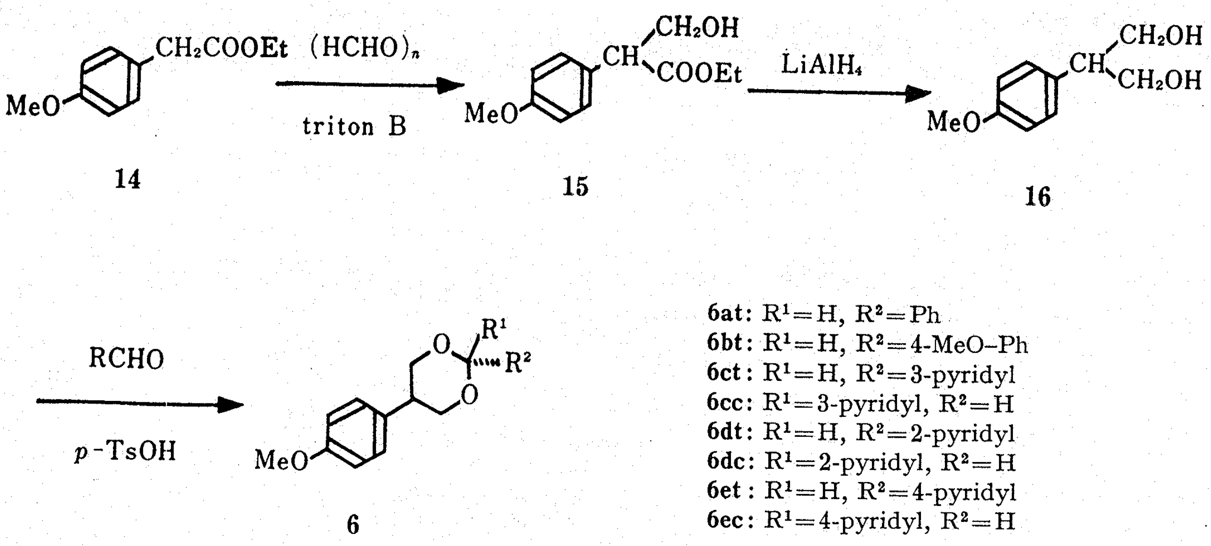
In addition, a comparison of the NMR spectra of **6ct** and **6cc** showed that the signal of the methine proton (C_5–H) in **6ct** appeared at lower field (0.45 ppm) than that in the latter. In contrast, the signal due to the *ortho*-protons (Ha) of the 5-phenyl group in **6cc** was observed at lower field (0.4 ppm) than that in the former. It has been generally assumed that (probably as a result of shielding by the ring oxygens of the 1,3-dioxane) the signal of axial C_5–H in **6ct** is shifted to lower field than that of equatorial C_5–H in **6cc**,⁹⁾ and this was also the case for the chemical shifts of the *ortho*-protons (Ha) of the axial and equatorial 5-phenyl groups in **6cc** and **6ct**.

Baumann⁹⁾ has demonstrated that the stable conformation of *cis*- and *trans*-2-pentadecyl-5-hydroxy-1,3-dioxane and related compounds is the chair form, and that the isomers differ in the orientation of their substitutents at C_5, while those at C_2 remain equatorially oriented. This suggested that the methine protons (C_2–H) in **6ct** and **6cc** are axially oriented. Thus, the compounds **6ct** and **6cc** were presumed to be the *trans* and *cis* isomers, respectively, as shown in Fig. 1.

The structures of the other 1,3-dioxanes (**6a**, **b**, **d**, **e**) were also established as the *trans* form on the basis of their NMR spectra. Their vicinal *J*-values between the methine protons (C_5–H) and the methylene protons (C_4–H_2 and C_6–H_2) were similar to those of **6ct**, as shown in Table I.

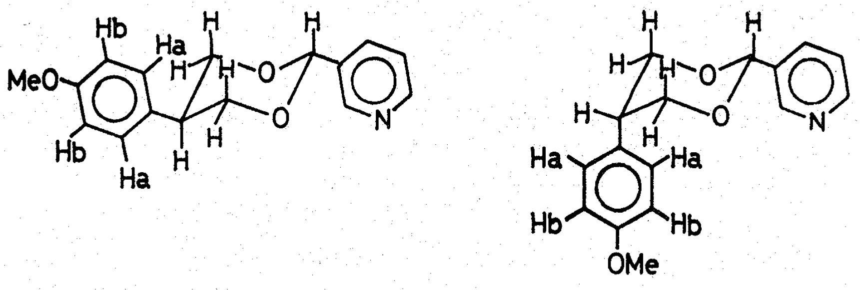
2-Substituted 5-(6-Methoxy-1,2,3,4-tetrahydro-2-naphthyl)-1,3-dioxanes (7)

Preparation of the intermediate (**20**) was carried out as shown in Chart 5. According to the method of Ungnard *et al.*,¹⁰⁾ catalytic reduction of 6-methoxy-2-naphthol (**10**) over



6at: $R^1=H$, $R^2=Ph$
6bt: $R^1=H$, $R^2=4\text{-MeO-Ph}$
6ct: $R^1=H$, $R^2=3\text{-pyridyl}$
6cc: $R^1=3\text{-pyridyl}$, $R^2=H$
6dt: $R^1=H$, $R^2=2\text{-pyridyl}$
6dc: $R^1=2\text{-pyridyl}$, $R^2=H$
6et: $R^1=H$, $R^2=4\text{-pyridyl}$
6ec: $R^1=4\text{-pyridyl}$, $R^2=H$

Chart 4



6ct **6cc**

Fig. 1

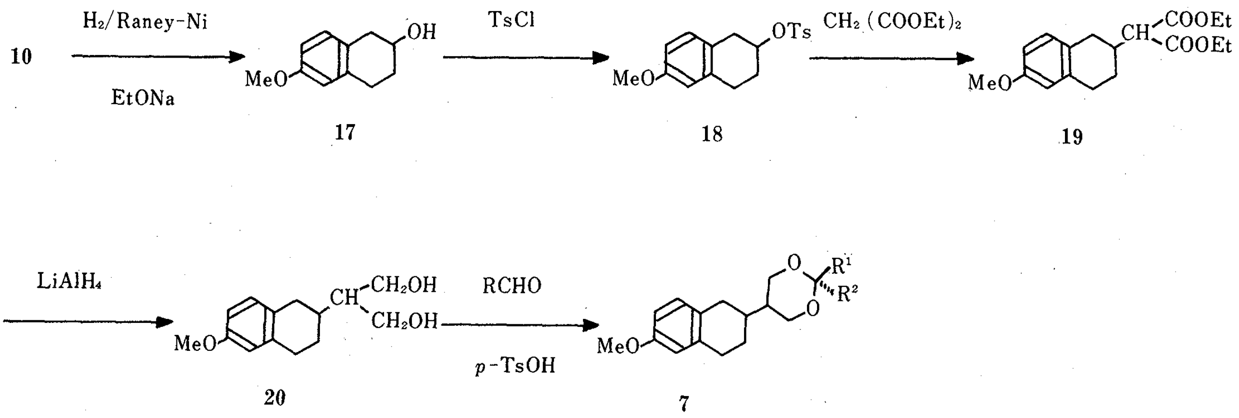
Table I. NMR Data for 2-Substituted 5-(4-Methoxyphenyl)-1,3-dioxanes (**6a**—**g**)

Compd. No.	Isomer	Chemical shift ($CDCl_3$, δ)				
		Methine	Methylene		J-value (Hz)	
		C_5–H	$C_{4,6}$–Ha	$C_{4,6}$–He[a]	$J_{5-4a,6a}$	$J_{5-4e,6e}$
6ct	*trans*	3.26(m)	3.96(t)	4.34(dd)	11.4	5.4
6cc	*cis*	2.81 (quint)	4.34(d)	4.34(d)	2.4	2.4
6at	*trans*	3.27(m)	3.97(t)	4.35(dd)	10.4	4.8
6bt	*trans*	3.26(m)	3.95(t)	4.34(dd)	10.8	5.4
6dt	*trans*	3.20(m)	4.00(t)	4.37(dd)	10.4	4.8
6et	*trans*	3.27(m)	3.96(t)	4.33(dd)	10.8	4.8
6ft	*trans*	[b]	3.72(t)	4.17(dd)	11.0	4.8
6gt HBr[c]	*trans*	[b]	3.95(t)	4.07(dd)	11.0	4.8

a) Ha: axial proton. He: equatorial proton.
b) Not determined.
c) Solvent: DMSO-d_6.

Raney Ni in the presence of EtONa afforded the 1,2,3,4-tetrahydro-2-naphthol (**17**). The compound **17** was converted to the tosylate (**18**), which was treated with diethyl malonate in the presence of *tert*-BuOK to give the diester (**19**). The diol (**20**) was obtained by reduction of **19** with $LiAlH_4$. The diol (**20**) was converted to the 1,3-dioxanes (**7a**—**h**) by treatment with the corresponding aromatic aldehydes in the same manner as in the case of **6**.

The 1,3-dioxanes (**7a**—**h**) were also obtained as mixtures of the stereoisomers. Among them, *trans*- (**7ct**) and *cis*-5-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)-2-(3-pyridyl)-1,3-



7at: R^1=H, R^2=Ph
7ac: R^1=Ph, R^2=H
7bt: R^1=H, R^2=4-MeO-Ph
7bc: R^1=4-MeO-Ph, R^2=H
7ct: R^1=H, R^2=3-pyridyl
7cc: R^1=3-pyridyl, R^2=H
7dt: R^1=H, R^2=2-pyridyl
7dc: R^1=2-pyridyl, R^2=H
7et: R^1=H, R^2=4-pyridyl
7ec: R^1=4-pyridyl, R^2=H
7ft: R^1=H, R^2=2-furyl
7fc: R^1=2-furyl, R^2=H
7gt: R^1=H, R^2=4,6-Cl_2-5-pyrimidinyl
7gc: R^1=4,6-Cl_2-5-pyrimidinyl, R^2=H
7ht: R^1=H, R^2=5-pyrimidinyl
7hc: R^1=5-pyrimidinyl, R^2=H

Chart 5

TABLE II. NMR Data for 2-Substituted 5-(6-Methoxy-1,2,3,4-tetrahydro-2-naphthyl)-1,3-dioxanes (**7a**—**h**) and 2-Substituted 5-(6-Methoxy-2-naphthyl)-1,3-dioxanes (**8a**, **b**)

Compd. No.	Isomer	Chemical shift ($CDCl_3$, δ)				
		Methine	Methylene		*J*-value (Hz)	
		C_5-H	$C_{4,6}$-Ha	$C_{4,6}$-He a)	$J_{5-4a,6a}$	$J_{5-4e,6e}$
7at	*trans*	b)	3.70(t)	4.41(dd)	11.0	4.6
7bt	*trans*	b)	3.70(t)	4.41(dd)	11.0	4.8
7ct	*trans*	b)	3.68(t)	4.37(dd)	11.0	4.8
7cc	*cis*	b)	4.04(dd)	4.36(dd)	2.4	2.0
7dt	*trans*	b)	3.75(t)	4.40(dd)	11.0	5.0
7et	*trans*	b)	3.71(t)	4.44(dd)	11.2	5.2
7ft	*trans*	b)	3.69(t)	4.41(dd)	11.0	4.8
7gt	*trans*	b)	3.72(t)	4.45(dd)	11.0	4.6
7ht	*trans*	b)	3.72(t)	4.44(dd)	11.0	4.8
8at	*trans*	3.45(m)	4.11(t)	4.45(dd)	11.2	5.2
8bt	*trans*	3.45(m)	4.12(t)	4.47(dd)	10.5	5.2

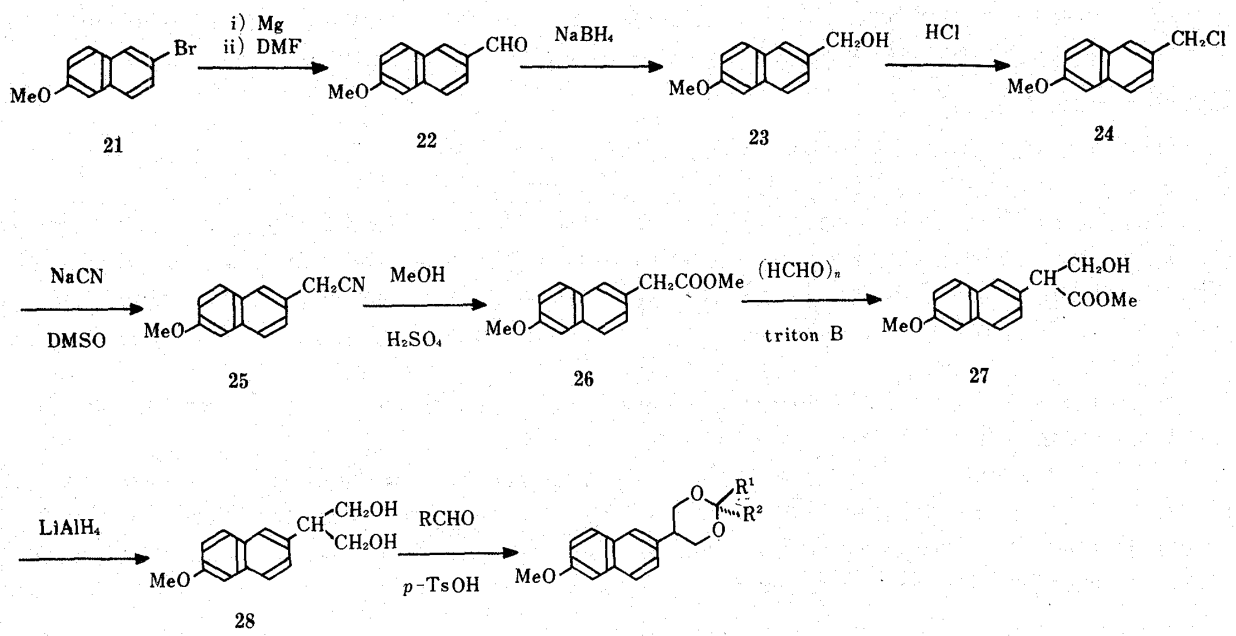
a) Ha: axial proton. He: equatorial proton.
b) Not determined.

dioxane (**7cc**) were isolated by repeated recrystallization in 43.6 and 33.2% yields, respectively.

The structures of **7a**—**h** were established on the basis of their NMR spectra, as shown in Table II.

2-Substituted 5-(6-Methoxy-2-naphthyl)-1,3-dioxanes (8)

The Grignard reaction of dimethylformamide with the arylmagnesium bromide prepared from 2-bromo-6-methoxynaphthalene (**21**) gave the aldehyde (**22**),11) which was reduced with $NaBH_4$ to the alcohol (**23**). Chlorination of **23** with hydrochloride, followed by treatment of the resulting chloride (**24**) with NaCN in DMSO, gave the nitrile (**25**). Methanolysis of **25** in the presence of sulfuric acid afforded the ester (**26**). The compound **26** was converted into the ester (**27**) and then into the diol (**28**), as described above. Reaction of **28** with the aromatic aldehydes gave the 1,3-dioxanes (**8a**, **b**) as mixtures of the *trans* and *cis* isomers.



8at: $R^1=H$, $R^2=$3-pyridyl
8ac: $R^1=$3-pyridyl, $R^2=H$
8bt: $R^1=H$, $R^2=$5-pyrimidinyl
8bc: $R^1=$5-pyrimidinyl, $R^2=H$

Chart 6

TABLE III. Hypolipidemic Activities[a] of 1,3-Dioxolane and 1,3-Dioxane Derivatives (**4**—**8**) in Normal Rats

Compd. No.	Relative potency[b]	
	Serum cholesterol	Serum triglyceride
4a	0	0
4b	0.13	0
4c	0	0
5a	0	0.73
6at	0.35	0
6bt	0	1.05
6ct	0.26	1.07
6cc	0	0
6dt	0.13	0.96
6et	0.55	0.17
6ft	0.15	0.23
6gt	0	0
7at	0.38	0
7bt	0	0
7ct	1.17	1.66
7cc	0	0
7dt	0.27	1.26
7et	0.49	0.71
7ft	0	0.33
7gt	0.13	0.17
7ht	0.84	0.99
8at	0.31	0.26
8bt	0.41	0.29

[a] The compounds were tested by administering 100 mg/kg/d, *p. o.*, for 3 d to male Wistar rats.

[b] Relative potencies are expressed as the ratio of the hypolipidemic activity to that of clofibrate taken as 1 (serum cholesterol 45.9%, serum triglyceride 40.2% reduction).

Only the *trans* isomers of **8a** and **8b** were isolated, and their structures were established by NMR spectroscopy, as shown in Table II.

Hypolipidemic Activity

The hypolipidemic activities of the 1,3-dioxolanes (**4**), 1,3-dioxin (**5**) and 1,3-dioxanes (**6**—**8**) are summarized in Table III.

The 1,3-dioxolanes (**4**) and 1,3-dioxin (**5**) showed little or no activity. The 1,3-dioxanes (**6**—**8**) having an aromatic ring at C_2, such as the pyridyl (**6c**—**e**, **7c**—**e** and **8a**) and pyrimidinyl (**7g**, **h** and **8b**) derivatives, had good hypolipidemic activities in the case of the *trans* isomers. However, exchange of the above heterocyclic groups for phenyl groups at C_2 of the 1,3-dioxanes (**6**—**7**) led to loss of either cholesterol or triglyceride lowering effects. The piperidine analogs (**6f**, **g**) were less active than the corresponding pyridine derivatives (**6c**, **d**). On the other hand, the *cis* isomers of **6cc** and **7cc** were completely inactive.

The most active compound in this study was **7ct**. In particular, this compound was found to have serum cholesterol and triglyceride lowering effects equivalent to those of clofibrate at doses of approximately one-third and one-seventh of that of clofibrate, respectively, in normal rats. No adverse effects such as estrogenic activity have been observed so far.

Experimental

All melting points (which were measured with a Yanagimoto melting point apparatus) and boiling points are uncorrected. IR spectra were taken with a Hitachi 285 spectrophotometer. NMR spectra were obtained on a Hitachi R-20B spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a Nihondenshi JMS-D300 spectrometer. All evaporation and concentration procedures were carried out *in vacuo*.

7-Methoxy-2-phenyl-3a,4,5,9b-tetrahydronaphtho[1,2-*d*]-1,3-dioxolane (**4a**)——A mixture of **9** (1.5 g, 7.73 mmol) and benzaldehyde diethylacetal (3.0 g, 17 mmol) was heated at 120—130°C for 30 min, then at 180—200°C for 2 h under a nitrogen atmosphere. After removal of the excess diethylacetal by evaporation, the residue was chromatographed on an alumina column with benzene to give **4a** (0.96 g, 43.7%) as a pale yellow oil. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1605, 1580, 1270, 1240, 1160, 1090, 1065, 1015, 875, 810, 760, 695. NMR ($CDCl_3$) δ: 1.85 (2H, m, 4-H_2), 2.70 (2H, m, 5-H_2), 3.69 (3H, s, OCH_3), 4.50 (1H, m, 3a-H), 5.06 (1H, d, $J=7$ Hz, 9b-H), 5.76 (1H, s, 2-H). *Anal.* Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.52; H, 6.44.

7-Methoxy-2-(4-methoxyphenyl)-3a,4,5,9b-tetrahydronaphtho[1,2-*d*]-1,3-dioxolane (**4b**)——A mixture of **9** (1.5 g, 7.73 mmol) and anisaldehyde diethylacetal (4.50 g, 21.4 mmol) was heated at 130—140°C for 1 h under a nitrogen atmosphere. After removal of the excess diethylacetal, the residue was crystallized from MeOH to afford **4b** (1.05 g, 44.1%) as colorless prisms, mp 87.5—88°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1605, 1580, 1255, 1250, 1180, 1170, 1110, 1080, 1070, 1030, 860, 830, 820. NMR ($CDCl_3$) δ: 1.87 (2H, m, 4-H_2), 2.77 (2H, m, 5-H_2), 3.75, 3.78 (each 3H, both s, $2\times OCH_3$), 4.56 (1H, m, 3a-H), 5.13 (1H, d, $J=7.5$ Hz, 9b-H), 5.83 (1H, s, 2-H). *Anal.* Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.28; H, 6.37.

7-Methoxy-2-(3-pyridyl)-3a,4,5,9b-tetrahydronaphtho[1,2-*d*]-1,3-dioxolane (**4c**)——A mixture of **9** (2.0 g, 10.3 mmol) and pyridine-3-aldehyde diethylacetal (3.0 g, 16.6 mmol) was heated at 140—160°C for 1 h under a nitrogen atmosphere. After removal of the excess diethylacetal, the residue was chromatographed on an alumina column with benzene–AcOEt (10:1) to give **4c** (1.38 g, 47.3%) as a yellow oil. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1605, 1580, 1270, 1240, 1165, 1155, 1130, 1080, 1040, 880, 865, 810, 715. NMR ($CDCl_3$) δ: 2.05 (2H, m, 4-H_2), 2.90 (2-H, m, 5-H_2), 3.71 (3H, s, OCH_3), 4.65 (1H, m, 3a-H), 5.21 (1H, d, $J=7$ Hz, 9b-H), 5.92 (1H, s, 2-H), 7.31 (1H, dd, $J=8$, 4.5 Hz, pyridine 5-H), 7.74 (1H, dt, $J=8$, 2 Hz, pyridine 4-H), 8.56 (1H, dd, $J=4.5$, 2 Hz, pyridine 6-H), 8.68 (1H, d, $J=2$ Hz, pyridine2-H). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.02; H, 6.01; N, 4.94. Found: C, 72.22; H, 6.01; N, 4.78.

2-Hydroxy-6-methoxy-1-naphthaldehyde (**11**)——Gaseous HCl was bubbled through a suspension of **10** (30 g, 0.172 mol) and $Zn(CN)_2$ (51 g, 0.43 mol) in dry Et_2O (500 ml) at -5°C with vigorous stirring for 1 h. Dry benzene (500 ml) was then added, and the whole was heated at 45—55°C for 2 h under stirring with further introduction of gaseous HCl. The reaction mixture was treated with 10% HCl (700 ml) and heated under reflux for 2 h. After cooling, the organic layer was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from MeOH to give **11** (27.9 g, 80.1%) as yellow needles, mp 131.5—132.5°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3420, 1620, 1275, 1250, 1180, 1170, 1150, 1080, 1030, 850, 820, 810, 740. NMR ($CDCl_3$) δ: 3.89 (3H, s, OCH_3), 7.08 (1H, d, $J=9$ Hz, 3-H), 7.10 (1H, d, $J=2.5$ Hz, 5-H), 7.26 (1H, dd, $J=8.5$, 2.5 Hz, 7-H), 7.85 (1H, d, $J=9$ Hz, 4-H), 8.16 (1H, d, $J=8.5$ Hz, 8-H), 10.72 (1H, s, CHO), 12.89 (1H, s, OH). *Anal.* Calcd for $C_{12}H_{10}O_3$: C, 71.29; H, 4.95. Found: C, 71.27; H, 5.13.

2-Hydroxy-1-hydroxymethyl-6-methoxynaphthalene (12)——A solution of NaBH$_4$ (2.25 g, 60 mmol) in H$_2$O (10 ml) was added dropwise to a solution of **11** (6.06 g, 30 mmol) in MeOH (160 ml), and the resulting solution was stirred at 0—5°C for 3.5 h under a nitrogen atmosphere. The solution was acidified with 10% AcOH at 0°C, diluted with H$_2$O and extracted with AcOEt. The extract was washed with 5% NaHCO$_3$ and H$_2$O, then dried and concentrated. The crystalline residue was recrystallized from benzene–cyclohexane to give **12** (5.09 g, 83.2%) as colorless scales, mp 102—103°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3360, 3300, 1240, 1160, 1070, 1020, 855, 845, 820. NMR (DMSO-d_6) δ: 3.83 (3H, s, OCH$_3$), 4.77 (1H, br s, CH$_2$–O$\underline{\text{H}}$), 4.97 (1H, s, C$\underline{\text{H}}_2$–OH), 7.10 (1H, dd, J=10, 2.5 Hz, 7-H), 7.12 (1H, d, J=9 Hz, 3-H), 7.15 (1H, d, J=2.5 Hz, 5-H), 7.59 (1H, d, J=9 Hz, 4-H), 7.96 (1H, d, J=10 Hz, 8-H), 9.45 (1H, s, Ar–OH). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.97. Found: C, 70.81; H, 6.00.

8-Methoxy-3-phenyl-1*H*-naphtho[2,1-*d*][1,3]dioxin (5a)——A solution of K (4.8 g, 120 mmol) in *tert*-BuOH (700 ml) was added dropwise to a solution of **12** (4.9 g, 24 mmol) and benzal chloride (19.3 g, 120 mmol) in *tert*-BuOH (500 ml) at 75—80°C with stirring under a nitrogen atmosphere, and then the mixture was heated under reflux for 1.5 h. After cooling, the reaction mixture was diluted with H$_2$O and extracted with benzene. The extract was washed with H$_2$O, then dried and concentrated. The residue was chromatographed on a silica gel column with benzene, then recrystallized from MeOH to give **5a** (0.47 g, 6.7%) as colorless needles, mp 159—160.5°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1600, 1250, 1230, 1160, 1090, 1010, 850, 815, 730, 700. NMR (CDCl$_3$) δ: 3.88 (3H, s, OCH$_3$), 5.38 (2H, s, CH$_2$–O), 6.00 (1H, s, 3-H), 7.04—7.67 (10H, m, Ar–H). *Anal.* Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 78.31; H, 5.54.

Condensation of the Diol (12) with Anisaldehyde Diethylacetal——A mixture of **12** (204 mg, 1 mmol) and anisaldehyde diethylacetal (630 mg, 3 mmol) was heated at 125—135°C for 2 h with vigorous stirring under a nitrogen atmosphere. The mixture was cooled, then the precipitate was filtered off and washed with a small amount of AcOEt. The product was subjected to preparative TLC (cyclohexane–AcOH (17: 3)) to give 8-methoxy-3-(4-methoxyphenyl)-1*H*-naphtho[2,1-*d*][1,3]dioxin (**5b**) and 1′,2′-dihydro-6,8′-dimethoxyspiro[naphthalene-1(2*H*),3′-[3*H*]naphtho[2,1-*b*]pyran]-2-one (**13**).

Recrystallization of **5b** from CHCl$_3$–MeOH afforded 5 mg (1.6%) of colorless scales, mp 167—169°C. NMR (CDCl$_3$) δ: 3.85, 3.90 (each 3H, both s, 2×OCH$_3$), 5.42 (2H, s, CH$_2$–O), 6.02 (1H, s, 3-H). MS *m*/*e*: 322 (M$^+$).

Recrystallization of **13** from AcOEt afforded 117 mg (62.9%) of yellow prisms, mp 155—156°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1675, 1280, 1270, 1230, 1170, 1120, 1080, 1040, 1005, 880, 860, 820, 810. NMR (CDCl$_3$) δ: 2.0—3.0 (4H, m, 3-H$_2$, 4-H$_2$), 3.82, 3.89 (each 3H, both s, 2×OCH$_3$), 6.11 (1H, d, J=9 Hz, 3′-H), 6.80—7.65 (9H, m, 4′-H, Ar–H). MS *m*/*e*: 372 (M$^+$), 186 (M$^+$/2). *Anal.* Calcd for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.57; H, 5.56.

Ethyl 3-Hydroxy-2-(4-methoxyphenyl)propionate (15)——A mixture of ethyl (4-methoxyphenyl)acetate (**14**) (7.95 g, 41 mmol), paraformaldehyde (1.27 g, 42.6 mmol), DMSO (8 ml) and a 40% methanolic solution of trimethylbenzylammonium hydroxide (0.8 g) was heated at 100°C with stirring for 1.5 h. After neutralization with AcOH, the solution was poured into H$_2$O and extracted with AcOEt. The extract was washed with 5% NaHCO$_3$ and H$_2$O, then dried and concentrated. The residue was chromatographed on a silica gel column with benzene–Et$_2$O (9: 1) to give **15** (4.52 g, 49.5%) as a colorless viscous oil, bp 142—143°C (0.2 mmHg). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 3430, 1720, 1605, 1580, 1250, 1180, 1030. NMR (CDCl$_3$) δ: 1.20 (3H, t, J=7.2 Hz, COOCH$_2$C$\underline{\text{H}}_3$), 2.84 (1H, s, CH$_2$–O$\underline{\text{H}}$), 3.66 (2H, d, J=4.2 Hz, C$\underline{\text{H}}_2$–OH), 3.77 (3H, s, OCH$_3$), 3.88 (1H, t, J=4.2 Hz, C$\underline{\text{H}}$–COOCH$_2$CH$_3$), 4.16 (2H, q, J=7.2 Hz, COOC$\underline{\text{H}}_2$CH$_3$), 6.85 (2H, d, J=9 Hz, phenyl 3,5-H), 7.19 (2H, d, J=9 Hz, phenyl 2,6-H).

2-(4-Methoxyphenyl)propane-1,3-diol (16)——A solution of **15** (4.27 g, 19.1 mmol) in dry THF (20 ml) was added dropwise to a suspension of LiAlH$_4$ (1.0 g, 26.4 mmol) in dry THF (10 ml) at 0—5°C and the mixture was stirred at room temperature for 5 h under a nitrogen atmosphere, poured into ice-cooled 10% HCl (50 ml) and extracted with AcOEt. The extract was washed with 5% NaHCO$_3$ and H$_2$O, then dried and concentrated. The residue was recrystallized from acetone–cyclohexane to give **16** (2.42 g, 69.8%) as colorless scales, mp 82—84°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3230, 1610, 1580, 835. NMR (CDCl$_3$) δ: 2.93 (1H, quint, J=6.6 Hz, –C$\underline{\text{H}}$(CH$_2$OH)$_2$), 3.29 (2H, br, –CH(CH$_2$–O$\underline{\text{H}}$)$_2$), 3.72 (3H, s, OCH$_3$), 3.85 (4H, d, J=6.6 Hz, –CH(C$\underline{\text{H}}_2$–OH)$_2$), 6.82 (2H, d, J=9 Hz, phenyl 3,5-H), 7.08 (2H, d, J=9 Hz, phenyl 2,6-H). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.19; H, 7.92.

5-(4-Methoxyphenyl)-2-(3-pyridyl)-1,3-dioxane (6c)——A mixture of **16** (3.0 g, 16.5 mmol), pyridine-3-aldehyde (2.1 g, 19.6 mmol) and *p*-TsOH H$_2$O (4.4 g, 23.1 mmol) in benzene (300 ml) was heated under reflux for 1 h with water separation by means of a Dean-Stark apparatus. After neutralization with 5% NaHCO$_3$, the solution was extracted with AcOEt. The extract was washed with H$_2$O, dried and concentrated. The residue was applied to a Florisil column and eluted with benzene–Et$_2$O (9: 1). The eluate was concentrated and the residue was recrystallized from acetone–cyclohexane to give the *trans* isomer (**6ct**) (3.26 g, 81%) as colorless crystals, mp 116.5—117.5°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1600, 1575, 1235, 1085, 1030, 840, 795, 715. NMR (CDCl$_3$) δ: 3.26 (1H, m, 5-H), 3.78 (3H, s, OCH$_3$), 3.96 (2H, t, J=11.4 Hz, 4,6-axH), 4.34 (2H, dd, J=11.4, 5.4 Hz, 4,6-eqH), 5.59 (1H, s, 2-H), 6.87 (2H, d, J=9 Hz, phenyl 3,5-H), 7.11 (2H, d, J=9 Hz, phenyl 2,6-H), 7.27 (1H, dd, J=7.8, 4.2 Hz, pyridine 5-H), 7.85 (1H, dt, J=7.8, 1.8 Hz, pyridine 4-H), 8.58 (1H, dd, J=4.2, 1.8 Hz, pyridine 6-H), 8.76 (1H, d, J=1.8 Hz, pyridine 2-H). *Anal.* Calcd for $C_{16}H_{17}NO_3$:

C, 70.83; H, 6.32; N, 5.16. Found: C, 70.59; H, 6.33; N, 5.15.

The mother liquor was twice subjected to preparative TLC with benzene–cyclohexane–Et_3N (9: 9: 2) to give additional **6ct** (0.19 g, 4.2%) and the *cis* isomer (**6cc**) (0.11 g, 2.5%) as colorless plates (cyclohexane), mp 105—106°C. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1610, 1595, 1580, 1250, 1130, 1030, 1010, 810, 800. NMR ($CDCl_3$) δ: 2.81 (1H, quint, J=2.4 Hz, 5-H), 3.80 (3H, s, OCH_3), 4.34 (4H, d, J=2.4 Hz, 4,6-H_2), 5.68 (1H, s, 2-H), 6.87 (2H, d, J=8.4 Hz, phenyl 3,5-H), 7.23 (1H, dd, J=7.8, 4.0 Hz, pyridine 5-H), 7.51 (2H, d, J=8.4 Hz, phenyl 2,6-H), 7.84 (1H, dt, J=7.8, 1.8 Hz, pyridine 4-H), 8.2—9.0 (2H, m, pyridine 2,6-H). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.63; H, 6.37; N, 4.99.

2-Substituted 5-(4-Methoxyphenyl)-1,3-dioxane (6a, b, d, e)——The *trans* isomers of **6a**, **b**, **d**, **e** were also prepared from **16** and the corresponding aldehydes in the manner described for the preparation of **6ct**. The results are listed in Table IV.

TABLE IV. *trans* Isomers of 2-Substituted 5-(4-Methoxyphenyl)-1,3-dioxanes (**6**)

Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
6at	Ph	83.5	119—120.5	$C_{17}H_{18}O_3$	75.53 (75.80	6.71 6.64	—
6bt	4-MeO–Ph	78.5	178.5—179.5	$C_{18}H_{20}O_4$	71.98 (72.16	6.71 6.69)	—
6dt	2-Pyridyl	33.5	103.5—104.5	$C_{16}H_{17}NO_3$	70.83 (70.60	6.32 6.32	5.16 5.36)
6et	4-Pyridyl	50.6	154—156	$C_{16}H_{17}NO_3$	70.83 (70.82	6.32 6.25	5.16 5.00)

***trans*-2-(1-Ethyl-3-piperidyl)-5-(4-methoxyphenyl)-1,3-dioxane (6ft)**——A solution of **6ct** (2.15 g) in EtI (20 ml) was allowed to stand at room temperature for 2 d. The precipitate was filtered off and washed with benzene to give an ethiodide of **6ct** (3.29 g, 97.6%). Recrystallization from EtOH–AcOEt afforded yellow needles, mp 165—166°C. *Anal.* Calcd for $C_{18}H_{22}INO_3$: C, 50.59; H, 5.19; I, 29.70; N, 3.28. Found: C, 50.75; H, 5.23; I, 29.93; N, 3.30. A solution of the ethiodide (2.0 g) in EtOH (80 ml) was hydrogenated over PtO_2 (200 mg) at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was neutralized with 5% $NaHCO_3$ and extracted with AcOEt. The extract was washed with H_2O, dried and chromatographed through an alumina column. After removal of the solvent by evaporation, the residue was crystallized from hexane to give **6ft**, mp 76—78°C. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1610, 1575, 1240, 1135. NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7.2 Hz, N-CH_2-$C\underline{H}_3$), 2.40 (2H, q, J=7.2 Hz, N-$C\underline{H}_2CH_3$), 3.72, (2H, t, J=11 Hz, 4,6-axH), 3.77 (3H, s, OCH_3), 4.17 (2H, dd, J=11, 4.8 Hz, 4,6-eqH),4.41 (1H, d, J=5.4 Hz, 2-H), 6.85 (2H, d, J=9 Hz, phenyl 3,5-H), 7.09 (2H, d, J=9 Hz, phenyl 2,6-H).

6ft. HBr; colorless needles (EtOH–AcOEt), mp 192—193°C. *Anal.* Calcd for $C_{18}H_{28}BrNO_3$: C, 55.96; H, 7.30; Br, 20.69; N, 3.63. Found: C, 56.09; H, 7.31; Br, 20.92; N, 3.61.

***trans*-2-(1-Ethyl-2-piperidyl)-5-(4-methoxyphenyl)-1,3-dioxane Hydrobromide (6gt.HBr)**——**6gt.HBr** was prepared from **6dt** in a 70.8% yield in the same manner as described for **6ft.HBr**. The analytical sample (recrystallized from EtOH–AcOEt) had mp 184.5—185.5°C (dec.). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 2640 (br), 1605, 1575, 1145, 1020. NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7.2 Hz, N-CH_2-$C\underline{H}_3$), 3.73 (3H, s, OCH_3), 3.95 (2H, t, J=11 Hz, 4,6-axH), 4.07 (2H, dd, J=11, 4.8 Hz, 4,6-eqH), 5.12 (1H, d, J=2.4 Hz, 2-H), 6.89 (2H, J=9 Hz, phenyl 3,5-H), 7.26 (2H, J=9 Hz, phenyl 2,6-H). *Anal.* Calcd for $C_{18}H_{28}BrNO_3$: C, 55.96; H, 7.30; Br, 20.69; N, 3.63. Found: C, 55.99; H, 7.21; Br, 20.94; N, 3.51.

6-Methoxy-2-(*p*-toluenesulfonyloxy)-1,2,3,4-tetrahydronaphthalene (18)——A solution of **10** (100 g, 0.575 mol) and Na (250 mg) in EtOH (500 ml) was hydrogenated over Raney Ni (20 g) at 120°C for 3 h. The initial pressure was 100 kg/cm^2. The catalyst was filtered off and the filtrate was concentrated. The residue was extracted with benzene. The extract was washed with 10% NaOH and H_2O, then dried and concentrated to give 6-methoxy-1,2,3,4-tetrahydro-2-naphthol (**17**) (101.8 g) as a yellow oil. NMR ($CDCl_3$) δ: 2.42 (1H, s, OH), 3.75 (3H, s, OCH_3), 4.10 (1H, m, 2-H).

A solution of the above crude **17** (101.8 g, 0.571 mol) and *p*-TsCl (158 g, 0.829 mol) in pyridine (500 ml) was allowed to stand at room temperature for 15 h. The mixture was diluted with H_2O and extracted with benzene. The extract was successively washed with 10% HCl, 5% $NaHCO_3$ and H_2O, then dried and concentrated. The residue was recrystallized from EtOH to give **18** (125 g, 65.5% overall from **10**) as colorless prisms, mp 97.5—98.5°C. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1610, 1600, 1580, 1170, 890. NMR ($CDCl_3$) δ: 2.47 (3H, s, Ar-CH_3), 3.77 (3H, s, OCH_3), 4.92 (1H, m, 2-H). *Anal.* Calcd for $C_{18}H_{20}O_4S$: C, 65.03; H, 6.06; S, 9.65. Found: C, 65.27; H, 6.10; S, 9.45.

2-(6-Methoxy-1,2,3,4-tetrahydro-2-naphthyl)propane-1,3-diol (20)——A solution of K (29.3 g, 0.749 mol) in *tert*-BuOH (700 ml) was added dropwise to a suspension of **18** (125 g, 0.376 mol) and diethyl malonate (120 g, 0.749 mol) in *tert*-BuOH (600 ml) and then the mixture was heated under reflux with stirring overnight. After neutralization with AcOH (50 g, 0.833 mol), the mixture was diluted with H_2O and extracted with benzene. The extract was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated to give the diester (**19**) (166.1 g) as a yellow oil.

A solution of the above compound **19** (166.1 g, 0.52 mol) in dry THF (700 ml) was added dropwise to a suspension of $LiAH_4$ (30 g, 0.791 mol) in dry THF (100 ml) at 0—5°C and the mixture was stirred at room temperature for 2 h, then heated under reflux with stirring overnight and worked up as described for the preparation of **16** to give crude **20**. Recrystallization from benzene afforded **20** (39.9 g, 44.9% overall form **18**) as colorless prisms, mp 84—85°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3300, 1605, 1570, 1260, 1025, 1005. NMR ($CDCl_3$) δ: 3.42 (2H, s, $CH(CH_2\text{–}O\underline{H})_2$), 3.75 (3H, s, OCH_3), 3.87 (4H, d, $J=5$ Hz, $CH(C\underline{H}_2\text{–}OH)_2$). *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.67; H, 8.53. Found: C, 71.36; H, 8.55.

5-(6-Methoxy-1,2,3,4-tetrahydro-2-naphthyl)-2-(3-pyridyl)-1,3-dioxane (7c)——A suspension of **20** (20 g, 84.7 mmol), pyridine-3-aldehyde (11 g, 102 mmol) and *p*-TsOH H_2O (19.8 g, 104 mmol) in benzene (600 ml) was refluxed with water separation by means of a Dean-Stark apparatus under a nitrogen atmosphere for 1 h. After cooling, the mixture was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated. The residual crystals were recrystallized from acetone–cyclohexane to give the *trans* isomer (**7ct**) (6.18 g, 22.4%) as colorless scales, mp 141—142°C. The mother liquor was concentrated and the residue was dissolved in MeOH (150 ml) containing conc. HCl (5.6 g). The solvent was evaporated off to afford the hydrochloride of **7ct** (8.39 g) as crystals, mp 221—224°C. This hydrochloride was treated with 5% $NaHCO_3$ and the mixture was extracted with AcOEt. The extract was washed with H_2O, dried and concentrated. The residual crystals were recrystallized from acetone–cyclohexane to give additional **7ct** (5.83 g, 21.2%), mp 140.5—141.5°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1605, 1575, 1260, 1135, 1085, 1015, 785, 710. NMR ($CDCl_3$) δ: 3.68 (2H, t, $J=11$ Hz, 4,6-axH), 3.72 (3H, s, OCH_3), 4.37 (2H, dd, $J=11$, 4.8 Hz, 4,6-eqH), 5.40 (1H, s, 2-H), 7.21 (1H, dd, $J=7.8$, 5 Hz, pyridine 5-H), 7.76 (1H, dt, $J=7.8$, 2 Hz, pyridine 4-H), 8.53 (1H, dd, $J=5$, 2 Hz, pyridine 6-H), 8.66 (1H, d, $J=2$ Hz, pyridine 2-H). *Anal.* Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.87; H, 7.26; N, 4.21.

The mother liquor of the preparation of the hydrochloride of **7ct** was concentrated and the residue was treated with 5% $NaHCO_3$. The mixture was extracted with AcOEt and the extract was washed with H_2O, dried and concentrated. Recrystallization from acetone–cyclohexane afforded the *cis* isomer (**7cc**) (9.13 g, 33%) as colorless needles, mp 122—123°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1600, 1590, 1255, 1150, 1000, 825, 795, 705. NMR ($CDCl_3$) δ: 3.74 (3H, s, OCH_3), 4.04 (2H, dd, $J=12$, 2.4 Hz, 4,6-axH), 4.36 (2H, dd, $J=12$, 2 Hz, 4,6-eqH), 5.56 (1H, s, 2-H), 7.21 (1H, dd, $J=7.8$, 5 Hz, pyridine 5-H), 7.76 (1H, dt, $J=7.8$, 2 Hz, pyridine 4-H), 8.53 (1H, dd, $J=5$, 2 Hz, pyridine 6-H), 8.64 (1H, d, $J=2$ Hz, pyridine 2-H). *Anal.* Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.93; H, 7.11; N, 4.31.

2-Substituted 5-(6-Methoxy-1,2,3,4-tetrahydro-2-naphthyl)-1,3-dioxanes (7a, b, d—h)——The *trans* isomers of **7a, b, d—h** were prepared from the diol (**20**) and the corresponding aldehydes in the same manner as described for the preparation of **7ct**. The results are presented in Table V.

Table V. *trans* Isomers of 2-Substituted 5-(6-Methoxy-1,2,3,4-tetrahydro-2-naphthyl)-1,3-dioxanes (7)

Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
7at	Ph	77.7	114—117	$C_{21}H_{24}O_3$	77.75 (77.91	7.46 7.45)	—
7bt	4-MeO–Ph	51.7	129—130	$C_{22}H_{26}O_4$	74.55 (74.51	7.39 7.54)	—
7dt	2-Pyridyl	38.9	144—146	$C_{20}H_{23}NO_3$	73.82 (73.60	7.12 7.19	4.30 4.36)
7et	4-Pyridyl	39.9	132—133	$C_{20}H_{23}NO_3$	73.82 (73.96	7.12 7.17	4.30 4.12)
7ft	2-Furyl	74.9	137.5—138	$C_{19}H_{22}O_4$	72.59 (72.80	7.06 7.16)	—
7gt	4,6-Cl_2-5-pyrimidinyl	49.8	146—147	$C_{19}H_{20}Cl_2N_2O_3$	57.73 (58.00	5.10 5.18	7.09 7.01)
7ht	5-Pyrimidinyl	93.9	149—154	$C_{19}H_{22}N_2O_3$	69.92 (70.01	6.79 6.82	8.58 8.51)

2-Hydroxymethyl-6-methoxynaphthalene (23)——A solution of Grignard reagent [prepared from 2-bromo-6-methoxynaphthalene (21) (200 g, 0.844 mol) and Mg (22.6 g, 0.928 mol) in dry THF (700 ml)] was added dropwise to a stirred solution of DMF (123.4 g, 1.69 mol) in dry THF (300 ml) at 0—5°C under a nitrogen atmosphere, and the solution was stirred at room temperature for 1 h then refluxed for 6 h. The reaction mixture was concentrated and the residue was poured into 5% H_2SO_4 (1000 ml). This solution was stirred at room temperature for 4 h to give crude 2-formyl-6-methoxy-naphthalene (**22**) as a precipitate. Additional **22** was obtained by extraction of the mother liquor with AcOEt. The compound **22** was recrystallized from $CHCl_3$–petroleum ether to give yellow prisms (110.3 g, 70.2%), mp 77—79°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1680 (CHO). NMR ($CDCl_3$) δ: 7.15—8.24 (6H, m, Ar–H), 10.10 (1H, s, CHO).

A solution of $NaBH_4$ (43.3 g, 1.14 mol) in H_2O (100 ml) was added dropwise to a stirred solution of **22** (141.2 g, 0.759 mol) in MeOH (1500 ml) at 0—5°C and the whole was stirred at room temperature for 2 h. After addition of 5% HCl (450 ml), the solution was extracted with AcOEt. The extract was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated. The crystalline residue was recrystallized from $CHCl_3$–cyclohexane to give **23** (130.9 g, 91.7%) as colorless plates, mp 123—124°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3250 (OH). NMR ($CDCl_3$) δ: 2.14 (1H, s, CH_2–O$\underline{H}$), 3.88 (3H, s, OCH_3), 4.74 (2H, s, C$\underline{H}_2$–OH), 7.04—7.75 (6H, m, Ar–H).

Methyl (6-Methoxy-2-naphthyl)acetate (26)——Gaseous HCl was bubbled through a suspension of **23** (130.9 g, 0.696 mol) in benzene (1500 ml) at 60°C with vigorous stirring for 2 h. The solution was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated. The residue was dissolved in DMSO (400 ml) and the solution was added to a suspension of NaCN (40.9 g, 0.835 mol) in DMSO (400 ml). The mixture was stirred at room temperature for 3 h and diluted with H_2O to give crude **25** as a precipitate. Additional **25** was obtained by extraction of the mother liquor with benzene. **25** was recrystallized from benzene–cyclohexane to give yellow prisms (109.8 g, 80.0%), mp 102—105°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2240 (CN). NMR ($CDCl_3$) δ: 3.81 (2H, s, CH_2–CN), 3.88 (3H, s, OCH_3).

Conc. H_2SO_4 (200 ml) was added to a solution of **25** (109.8 g, 0.55 mol) in MeOH (700 ml) and the solution was refluxed for 6 h. After cooling, the solution was poured into ice-water (5000 ml) and the whole was extracted with benzene. The extract was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated. The residue was chromatographed on an alumina column with benzene–cyclohexane (1 : 1). Concentration of the eluate yielded a crystalline residue, which was recrystallized from benzene–cyclohexane to give **26** (82.2 g, 64.1%) as light yellow prisms, mp 70—73°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1725 ($COOCH_3$). NMR ($CDCl_3$) δ: 3.69 (3H, s, $CH_2COOC\underline{H}_3$), 3.75 (2H, s, $C\underline{H}_2COOCH_3$), 3.88 (3H, s, OCH_3).

2-(6-Methoxy-2-naphthyl)propane-1,3-diol (28)——A mixture of **26** (10 g, 43.5 mmol), paraformaldehyde (1.96 g, 65.3 mmol), 40% methanolic solution of trimethylbenzylammonium hydroxide (0.7 ml) and DMSO (35 ml) was heated at 100°C with stirring for 1 h. After neutralization with AcOH, the solution was diluted with H_2O (300 ml) and extracted with AcOEt. The extract was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated. The residue was chromatographed on a silica gel column with benzene–AcOEt (4 : 1) to give **27** (8.07 g, 71.4%) as a colorless crystalline powder (from benzene–cyclohexane), mp 86.5—89°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3450 (OH), 1730 ($COOCH_3$). NMR ($CDCl_3$) δ: 2.36 (1H, br s, CH_2–O$\underline{H}$), 3.72 (3H, s, $COOH_3$), 3.90 (3H, s, OCH_3), 4.02 (2H, d, J=3.5 Hz, C$\underline{H}_2$–OH), 4.13 (1H, t, J=3.5 Hz, –C$\underline{H}$–$COOH_3$).

A solution of **27** (12.9 g, 49.7 mmol) in dry THF (200 ml) was added dropwise to a suspension of $LiAlH_4$ (2.83 g, 74.6 mmol) in dry THF (20 ml) at 0—5°C with vigorous stirring under a nitrogen atmosphere. The suspension was stirred at room temperature for 5 h. After addition of 10% HCl (100 ml) below 10°C, the solution was extracted with AcOEt. The extract was washed with 5% $NaHCO_3$ and H_2O, then dried and concentrated. The crystalline residue was recrystallized from AcOEt–benzene to give **28** (8.88 g, 77.0%) as colorless scales, mp 136—139°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3220, 1270, 1210, 1170, 1120, 1060, 1040, 1020, 890, 850, 815. NMR (acetone-d_6) δ: 2.43 (2H, s, $CH(CH_2$–O$\underline{H})_2$), 3.13 (1H, quint, J=6 Hz, –C$\underline{H}$(CH_2–OH$)_2$), 3.89 (3H, s, OCH_3), 3.94 (4H, d, J=6 Hz, –CH(C$\underline{H}_2$–OH$)_2$). *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.63; H, 7.11.

5-(6-Methoxy-2-naphthyl)-2-(3-pyridyl)-1,3-dioxane (8a)——A suspension of **28** (2.0 g, 8.62 mmol), pyridine-3-aldehyde (1.11 g, 10.3 mmol) and p-TsOH H_2O (2.07 g, 10.9 mmol) in benzene (200 ml) was refluxed with water separation by means of a Dean-Stark apparatus. After cooling, the solution was washed with 5% $NaHCO_3$ and H_2O, then dried and passed through an alumina column. Concentration of the eluate and recrystallization of the residue from acetone–cyclohexane gave the *trans*-isomer (**8at**) (1.15 g, 41.7%) as colorless prisms, mp 167—172°C. A further recrystallization from MeOH afforded an analytical sample as colorless needles, mp 171—173°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1270, 1230, 1155, 1130, 1075, 1010, 890, 850, 810, 795, 705. NMR ($CDCl_3$) δ: 3.45 (1H, m, 5-H), 3.91 (1H, s, OCH_3), 4.11 (2H, d, J=11.2 Hz, 4,6-axH), 4.45 (2H, dd, J=11.2, 5.2 Hz, 4,6-eqH), 5.65 (1H, s, 2-H), 7.23 (1H, dd, J=8, 4.5 Hz, pyridine 5-H), 7.89 (1H, dt, J=8, 2.5 Hz, pyridine 4-H), 8.60 (1H, dd, J=4.5, 2.5 Hz, pyridine 6-H), 8.79 (1H, d, J=2.5 Hz, pyridine 2-H). *Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.76; H, 5.96; N, 4.36. Found: C, 75.07; H, 5.96; N, 4.45.

5-(6-Methoxy-2-naphthyl)-2-(5-pyrimidinyl)-1,3-dioxane (8b)——The crude *trans* isomer (**8bt**) was prepared from **28** (500 mg, 2.16 mmol) and pyridine-5-aldehyde (280 mg, 2.59 mmol) in the same manner as described for the preparation of **8at**. The crude product was subjected to column chromatography on silica gel with benzene–AcOEt (4 : 1) to give **8bt** (397 mg, 57.2%) as a colorless crystalline powder, which was recrystallized from AcOEt–MeOH, mp 206—208.5°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1630, 1270, 1260, 1230, 1210, 1160, 1105, 1080, 1010, 850, 810, 725. NMR ($CDCl_3$) δ: 3.45 (1H, m, 5-H), 3.90 (3H, s, OCH_3), 4.12 (2H, t, $J=$ 10.5 Hz, 4,6-axH), 4.47 (2H, dd, $J=10.5$, 5.2 Hz, 4,6-eqH), 5.68 (1H, s, 2-H), 8.91 (2H, s, pyrimidine 4,6-H), 9.25 (1H, s, pyrimidine 2-H). *Anal.* Calcd for $C_{19}H_{18}N_2O_2$: C, 70.79; H, 5.53; N, 8.69. Found: C, 70.56; H, 5.77; N, 8.57.

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References and Notes

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