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Studies on Antidiabetic Agents. IV.[1] Synthesis and Activity of the Metabolites of 5-[4-(1-Methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (Ciglitazone)

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Compounds **2**—**9** possessing a hydroxy or an oxo moiety on the cyclohexane ring of 5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (**1**, ciglitazone) were synthesized to clarify the structure of the metabolites of **1** and for studies of their pharmacological properties. Of the metabolites identified, 5-[4-(*t*-3-hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (**7**) exhibited extremely potent antidiabetic activity compared to **1**. Stereoselective syntheses of 3- or 4-hydroxy-1-methylcyclohexanecarboxylic acids required for the preparation of 3′- or 4′-hydroxylated compounds (**6**, **7** or **3**, **4**, respectively) are described.

Keywords——antidiabetic agent; ciglitazone metabolite; 3-aryl-2-halopropionic acid; 1-methylcyclohexanecarboxylic acid derivative; 2,4-thiazolidinedione

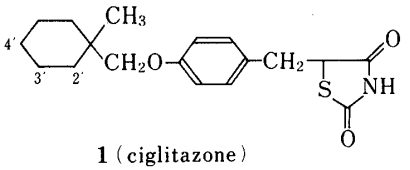
In a previous paper,[2] we reported the synthesis of 5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (**1**, ciglitazone[3]), which exhibits remarkable hypoglycemic and hypolipidemic activities in a screening system using KKA^y mice.[4] The metabolic fate of this compound has been investigated by Tanayama, Itakura and their co-workers and five metabolites were found in the plasma and urine of rats, dogs and men given ciglitazone.[5] Structures having a hydroxy or an oxo moiety at a certain position (2′,3′ or 4′) on the cyclohexane ring of **1** were proposed for the metabolites on the basis of mass spectroscopic analysis. All candidates (**2**—**9**) (Fig. 1) for the metabolites were prepared in order to unambiguously determine the structures and so that studies of their pharmacological properties could be carried out.

In general, the compounds (**2**—**9**) were synthesized starting from 1-methylcyclohexanemethanols (III) bearing a protected hydroxy or ketone, as shown in Chart 1. The alcohols (III) were condensed with *p*-chloro- or *p*-fluoronitrobenzene and deprotected to give the nitro compounds (V). Treatment of IV or V according to the same procedure as used for the preparation of **1**[2] (four reaction steps) gave the desired compounds (**2**—**9**).

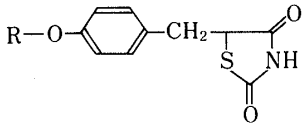
Synthesis of the 4′-oxo (2), *cis*-4′-ol (3) and *trans*-4′-ol (4) Compounds

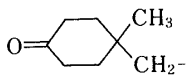
Methyl 1-methyl-4-oxocyclohexanecarboxylate (**11**), prepared by catalytic reduction of methyl 1-methyl-4-oxo-2-cyclohexenecarboxylate (**10**),[6] was converted into the alcohol (**12**) by the usual method. When hydrogenated over PtO_2 in acetic acid, **11** gave a mixture of *cis*- and *trans*-4-hydroxy-1-methylcyclohexanecarboxylic acid esters **13** and **14** in a ratio of 4.1 : 1. The major *cis* alcohol (**13**) was purified as the hydroxy acid (**16**), which was converted into the alcohol (**17**) by the usual method. The configuration of the hydroxyl group at C-4 in **16** was confirmed by its lactonization to **15**[7] (Chart 2).

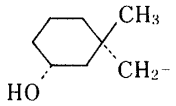
The *trans*-alcohol (**14**) was successfully synthesized as shown in Chart 3. Oxymercuration[8] of **18**[9] followed by reduction with $NaBH_4$ afforded only the *trans*-4-hy-

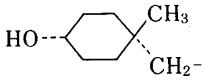


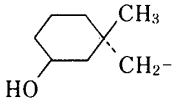
1 (ciglitazone)

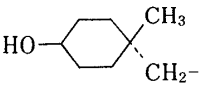


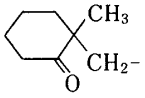
2 : R =  (4′-oxo)

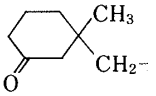
6 : R =  (*cis*-3′-ol)

3 : R =  (*cis*-4′-ol)

7 : R =  (*trans*-3′-ol)

4 : R =  (*trans*-4′-ol)

8 : R =  (2′-oxo)

5 : R =  (3′-oxo)

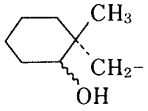
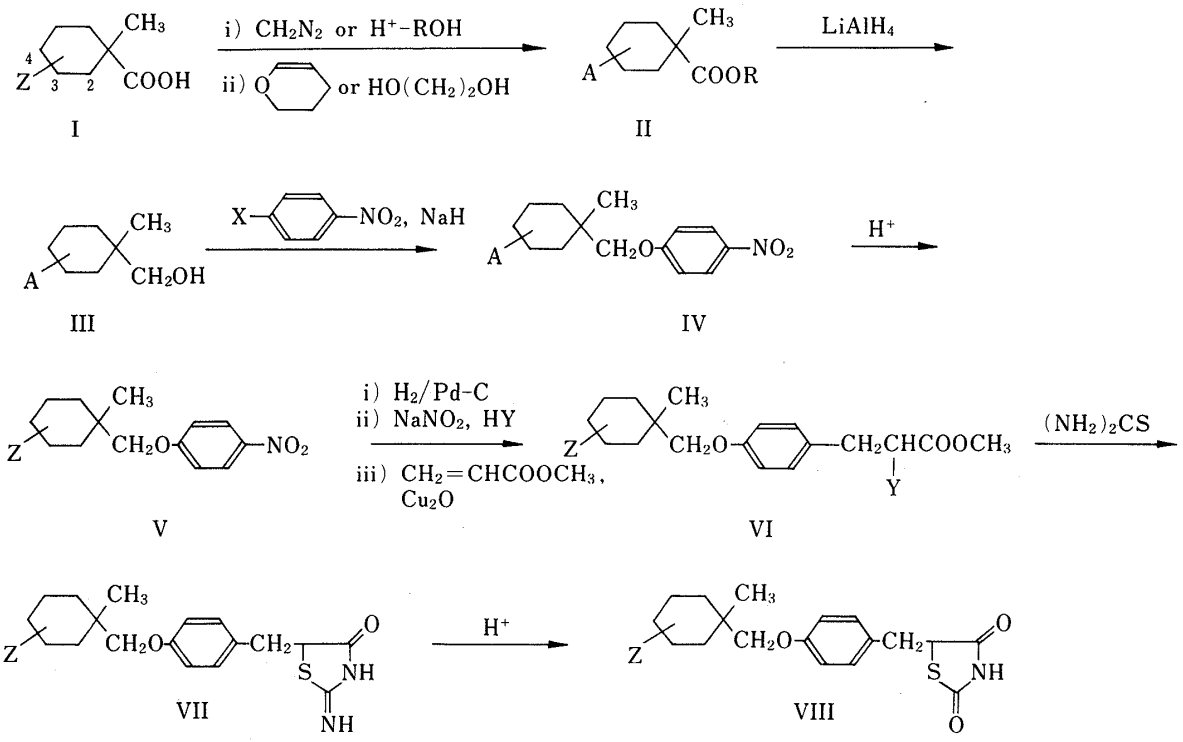
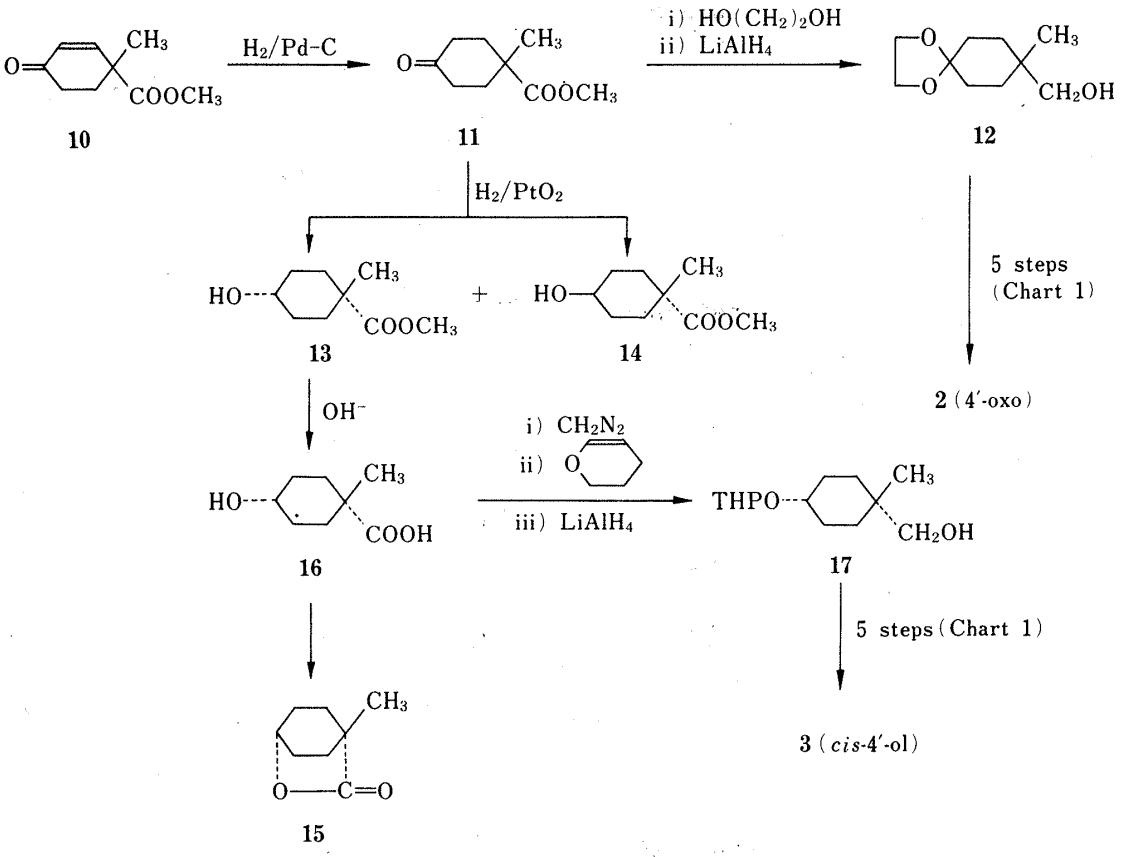
9 : R =  (2′-ol)

Fig. 1



A = ethylenedioxy or 2-tetrahydropyranyloxy, R = CH_3 or C_2H_5, X = F or Cl, Y = Br or Cl, Z = oxo or hydroxy

Chart 1



THP = 2-tetrahydropyranyl

Chart 2

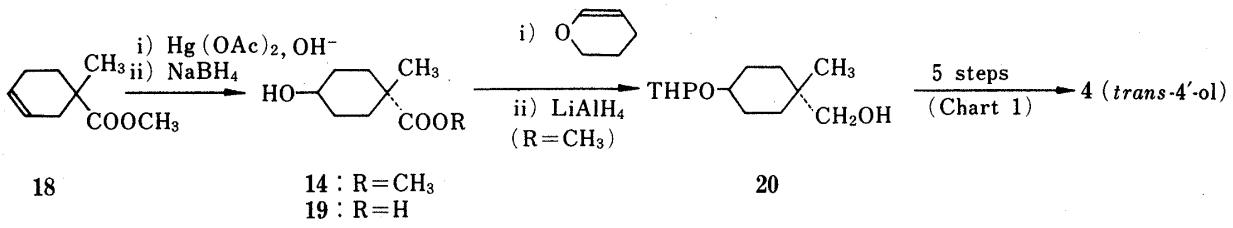


Chart 3

droxy isomers (**14**+**19**) in 70% total yield. High regio- and stereoselectivities are sometimes found in the oxymercuration-reduction.[8] The stereospecificity seen in this case seems to be due to the attack of the hydroxyl anion from the least sterically-hindered site of the intermediate mercurinium ion. Compounds **14** and **19** thus obtained were converted into the alcohol (**20**) by the usual method.

Compounds **12**, **17** and **20** were subjected to the sequence in Chart 1 to yield **2**, **3** and **4**, respectively. Reduction of **2** with $NaBH_4$ afforded an inseparable mixture of **3** and **4** in a ratio of 1 : 2.[10]

Synthesis of the 3'-oxo (5), *cis*-3'-ol (6) and *trans*-3'-ol (7) Compounds

Several routes were used for the synthesis of methyl 1-methyl-3-oxocyclohexanecarboxylate (**24**) as shown in Chart 4. In these methods, the intermediate compounds **21** and **23** were obtained as mixtures of the regio- and/or stereoisomers, but were used in the subsequent reactions without purification. The lack of regio- and/or stereoselectivity resulted in the low yield of **24** in these reactions. Compound **24** thus obtained was con-

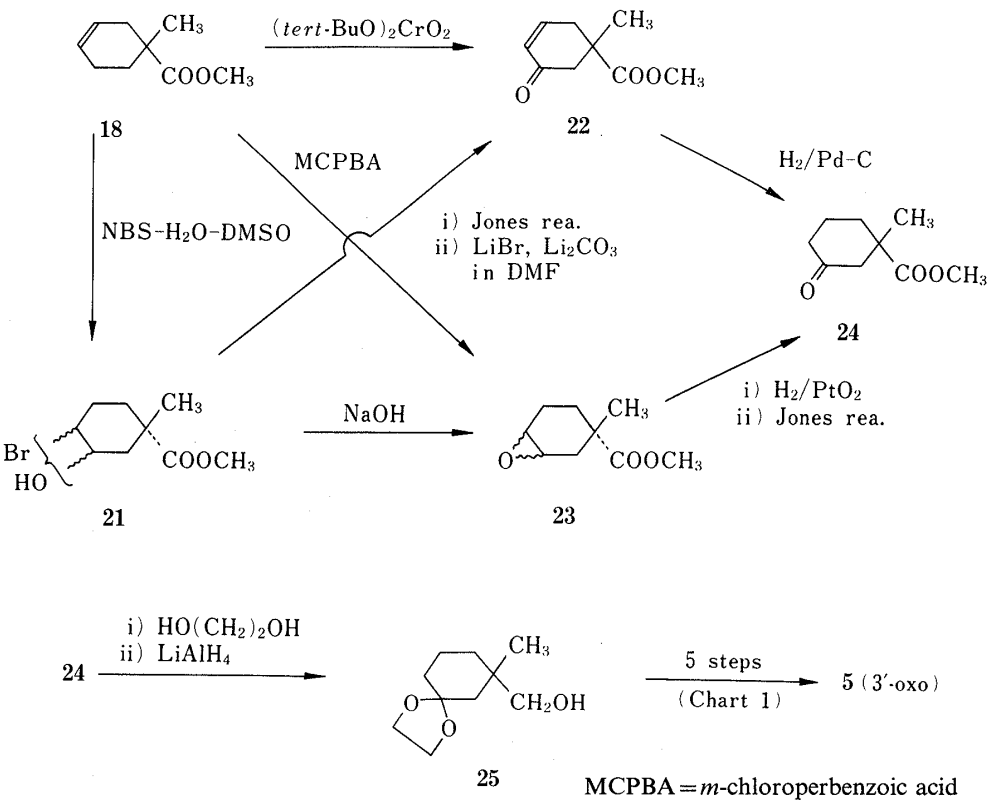


Chart 4

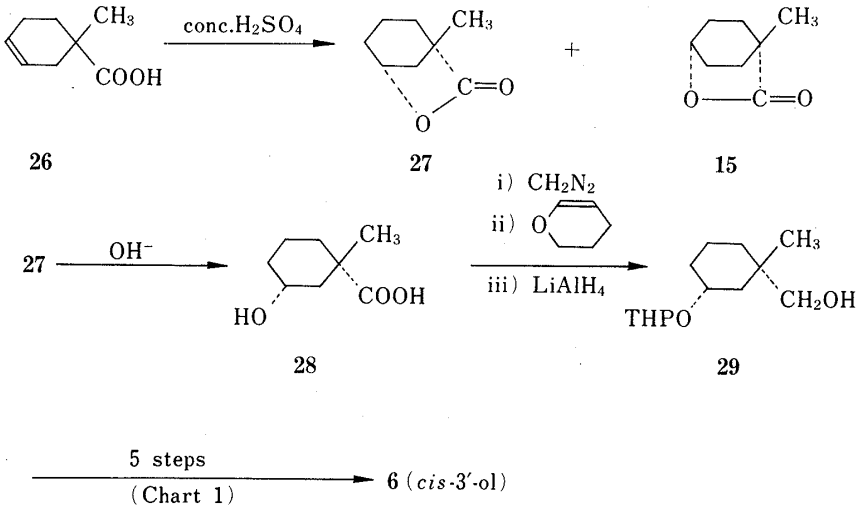


Chart 5

verted to the alcohol (**25**) and then subjected to the sequence in Chart 1 to afford the 3′-oxo compound (**5**)[11] (Chart 4).

Since stereoselective reduction of **5** or **24** appeared to be unsuccessful, alternative stereoselective methods to prepare the *cis*-3′-ol (**6**) and *trans*-3′-ol (**7**) were sought. When 1-methyl-3-cyclohexenecarboxylic acid (**26**)[12] was treated with conc. H_2SO_4, the γ-lactone (**27**) was obtained in 60% yield along with a small amount of the δ-lactone (**15**).[7] Alkaline hydrolysis of **27** afforded the *cis*-hydroxy acid (**28**), which was converted into the alcohol (**29**) by the usual method (Chart 5).

Methylation of methyl 3-(2-tetrahydropyranyloxy)cyclohexanecarboxylate (**30**), on the

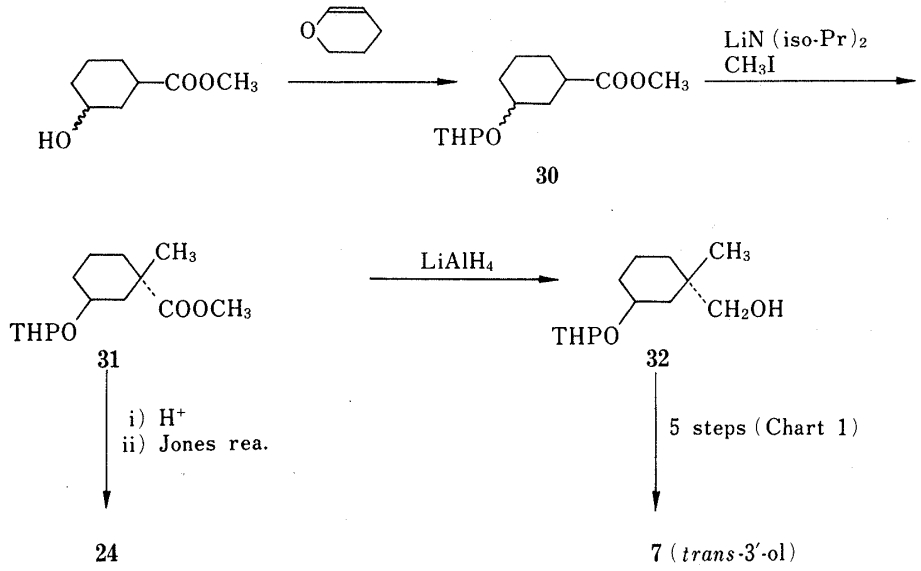


Chart 6

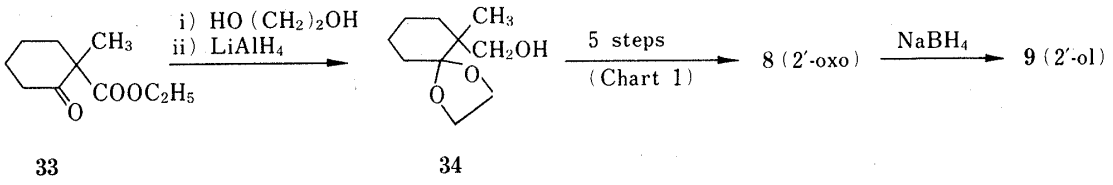


Chart 7

other hand, gave the single *trans*-isomer (**31**) in a high yield (Chart 6). Gas chromatographic analysis of the methylated product showed no contamination by the *cis*-isomer. Although Krapcho *et al.*[7] reported that methylation of methyl 3-methoxycyclohexanecarboxylate afforded a product mixture favoring the equatorially methylated compound in a ratio of 78 : 22, the stereospecificity seen in the methylation of **30** was a rather unexpected result. Compound **31** was converted into the alcohol (**32**) by the usual method. Compound **31** was also converted into **24** in good yield by treatment with dil. HCl followed by Jones oxidation. This method provides a better protocol for the synthesis of **24** than that shown in Chart 4.

Compounds **29** and **32** were subjected to the sequence in Chart 1 to afford the *cis*-3′-ol (**6**)[11] and *trans*-3′-ol (**7**),[11] respectively.

Synthesis of the 2′-oxo (8) and 2′-ol (9) Compounds

Ketalization of ethyl 1-methyl-2-oxocyclohexanecarboxylate (**33**)[13] followed by reduction gave the alcohol (**34**), which was subjected to the sequence in Chart 1 to afford the 2′-oxo compound (**8**).[11] Reduction of **8** with $NaBH_4$ gave the 2′-ol (**9**)[11] as an isomeric mixture, but no attempt was made to isolate each isomer because the 2′-hydroxy derivative was found only as a minor metabolite of ciglitazone.[5]

The metabolites of ciglitazone (**1**) were confirmed to be the 4′-oxo (**2**), *cis*-4′-ol (**3**), *trans*-4′-ol (**4**), 3′-oxo (**5**),[11] *cis*-3′-ol (**6**),[11] *trans*-3′-ol (**7**)[11] and 2′-ol (**9**)[11] compounds by direct comparison [thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC) and mass spectroscopy (MS)] with the authentic compounds prepared in this study.[5]

The antidiabetic activities of compounds **2**—**9** in genetically obese and diabetic mice, yellow KK,[4] are shown in Table I.[14] All metabolites, especially the *trans*-3′-ol (**7**),[11] which is one of the main metabolites in men,[5] showed potent hypoglycemic and hypolipidemic

TABLE I. Biological Properties of the Metabolites of Ciglitazone

Compound No.	Hypoglycemic activity[a]	Plasma triglyceride-lowering activity[a]
2 (4′-oxo)	1	1
3 (*cis*-4′-ol)	1	0
4 (*trans*-4′-ol)	2	1
5 (3′-oxo)	1	1
6 (*cis*-3′-ol)	1	2
7 (*trans*-3′-ol)	3	3
8 (2′-oxo)[b]	3	2
9 (2′-ol)	2	1
1 (Ciglitazone)	1	1

a) Maximum reductions in blood glucose and plasma triglyceride levels at the dosage of 0.02% (w/w) in the diet were calculated as percentages of the control value. The following activity ranks are used here; 50—69% reduction = 3, 30—49% reduction = 2, 10—29% reduction = 1, less than 9% = 0.
b) This compound has not been found as a metabolite.

activities. This result suggests that these metabolites must contribute, at least in part, to the pharmacological action of ciglitazone (**1**). It is also noteworthy that the 2′-oxo compound (**8**),[11] which has not been found as a metabolite, showed very potent activity.

Experimental

All melting points were determined on a Yanagimato micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 or a Varian T-60 spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm with Me_4Si as an internal standard, and the following abbreviations are used: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on a JEOL JMS-01SC mass spectrometer. Analyses by gas-liquid chromatography (GLC) were conducted on a JEOL JGC-20K gas chromatograph equipped with a flame-ionization detector using a column of 5% ECNSS-M on Gas Chrom Q (80—200 mesh, 2.0 × 2 m). The apparatus used for HPLC was a Yanaco L-1030 high-performance liquid chromatograph equipped with a Yanagimoto M-215 spectromonitor.

Methyl 1-Methyl-4-oxocyclohexanecarboxylate (11)——A mixture of methyl 1-methyl-4-oxo-2-cyclohexenecarboxylate[6] (**10**) (100.0 g), 10% Pd–C (50% wet, 5.0 g) and AcOEt (600 ml) was hydrogenated at room temperature and 1 atm. The catalyst was removed by filtration, and the filtrate was distilled to give **11** as an oil (96.5 g, 95.4%), bp 82—84 °C/0.5 mmHg. IR ν_{max}^{neat} cm^{-1}: 1730, 1715. NMR δ: 1.32 (3H, s), 1.5—2.7 (8H, m), 3.80 (3H, s). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.11; H, 8.41.

4,4-Ethylenedioxy-1-methylcyclohexanemethanol (12)——A mixture of **11** (30.0 g), ethylene glycol (30.0 ml), *p*-TsOH (1.0 g) and C_6H_6 (300 ml) was refluxed with continuous removal of the resulting H_2O for 3 h, then washed with H_2O, dried ($MgSO_4$) and concentrated to give an oily ethyleneacetal of **11** (37.8 g, quant.). IR ν_{max}^{neat} cm^{-1}: 1720. NMR δ: 1.20 (3H, s), 1.4—2.4 (8H, m), 3.70 (3H, s), 3.95 (4H, s). The oil was dissolved in Et_2O (50 ml) and the solution was added dropwise to a stirred suspension of $LiAlH_4$ (6.7 g) in Et_2O (200 ml) at room temperature. The mixture was stirred at room temperature for 1 h and the usual work-up gave **12** (29.5 g, 89.9%), bp 120—125 °C/0.5 mmHg. IR ν_{max}^{neat} cm^{-1}: 3230. NMR δ: 0.97 (3H, s), 1.3—1.9 (8H, m), 2.90 (1H, t, J = 5), 3.42 (2H, d, J = 5), 4.00 (4H, s). *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.09; H, 9.81.

4-(4,4-Ethylenedioxy-1-methylcyclohexylmethoxy)nitrobenzene——A stirred mixture of **12** (28.8 g), *p*-fluoronitrobenzene (21.8 g) and DMSO (250 ml) was treated with 60% NaH in oil (6.8 g) at room temperature for 2 h. The reaction mixture was poured into ice-H_2O and extracted with Et_2O. The usual work-up of the Et_2O extract gave the title compound as crystals (41.5 g, 87.2%). Recrystallization from MeOH gave colorless prisms, mp 78—79 °C. IR ν_{max}^{Nujol} cm^{-1}: 1585, 1340. NMR δ: 1.09 (3H, s), 1.7 (8H, br s), 3.78 (2H, s), 3.94 (4H, s), 6.97 (2H, d, J = 9), 8.20 (2H, d, J = 9). *Anal.* Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.37; H, 6.77; N, 4.40.

Methyl 2-Chloro-3-[4-(1-methyl-4-oxocyclohexylmethoxy)phenyl]propionate——A mixture of 4-(4,4-ethylenedioxy-1-methylcyclohexylmethoxy)nitrobenzene (30.0 g), 10% Pd–C (50% wet, 3.0 g) and MeOH (300 ml) was hydrogenated at room temperature and 1 atm. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in acetone (300 ml). Conc. HCl (24.5 ml) and a solution of

$NaNO_2$ (7.44 g) in H_2O (15 ml) were added dropwise to the stirred and ice-cooled solution below 5 °C. The whole was stirred at 5 °C for 30 min, then methyl acrylate (50.6 g) was added thereto and the temperature was raised to 35 °C. Cu_2O (0.8 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The usual work-up gave a crude oil which was purified by column chromatography on silica gel (400 g) using Et_2O–hexane (1 : 2, v/v) as an eluent to give the title compound as a pure oil (19.5 g, 58.7%). IR ν_{max}^{neat} cm^{-1}: 1740, 1705. NMR δ: 1.21 (3H, s), 1.6—2.1 (4H, m), 2.1—2.6 (4H, m), 3.06 (1H, q, J=14 and 7), 3.38 (1H, q, J=14 and 7), 3.74 (3H, s), 3.80 (2H, s), 4.46 (1H, t, J=7), 6.90 (2H, d, J=9), 7.21 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{23}ClO_4$: C, 63.81; H, 6.84. Found: C, 63.91; H, 6.92.

5-[4-(1-Methyl-4-oxocyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (2, 4'-oxo)——A mixture of methyl 2-chloro-3-[4-(1-methyl-4-oxocyclohexylmethoxyl)phenyl]propionate (19.2 g), thiourea (6.5 g) and sulfolane (180 ml) was stirred at 120 °C for 12 h and 2 N HCl (150 ml) was added thereto. After being stirred at 100 °C for 12 h, the mixture was diluted with H_2O and extracted with Et_2O. The usual work-up of the Et_2O extract gave an oily residue, which was chromatographed on silica gel (300 g) with AcOEt–hexane (2 : 3, v/v) to give **2** as crystals (14.0 g, 70.7%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 135—136 °C. IR ν_{max}^{Nujol} cm^{-1}: 3200, 3050, 1745, 1705, 1670. NMR δ: 1.23 (3H, s), 1.6—2.2 (4H, m), 2.3—2.6 (4H, m), 3.07 (1H, q, J=14 and 10), 3.46 (1H, q, J=14 and 5), 3.77 (2H, s), 4.51 (1H, q, J=10 and 5), 6.86 (2H, d, J=9), 7.17 (2H, d, J=9), 9.1 (1H, br s). *Anal.* Calcd for $C_{18}H_{21}NO_4S$: C, 62.24; H, 6.10; N, 4.03. Found: C, 62.44; H, 6.07; N, 4.44.

***c*-4-Hydroxy-1-methyl-*r*-1-cyclohexanecarboxylic Acid (16)**——A mixture of **11** (5.0 g), PtO_2 (0.6 g) and AcOH (50 ml) was hydrogenated at room temperature and 1 atm. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH (30 ml), then 2 N KOH (20 ml) was added, and the mixture was refluxed for 1 h, diluted with H_2O, acidified with conc. HCl and extracted with AcOEt. The usual work-up of the extract gave a crystalline residue. Recrystallization from AcOEt gave **16** as colorless prisms (2.35 g, 50.5%), mp 164—165 °C. IR ν_{max}^{Nujol} cm^{-1}: 3430, 1690. NMR (d_6-DMSO) δ: 1.07 (3H, s), 1.2—2.1 (8H, m), 3.37 (1H, m). *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 61.11; H, 8.59.

1-Methylcyclohexane-1,4-carbolactone (15)——A mixture of **13** (0.517 g), *p*-TsOH (0.01 g) and C_6H_6 (15 ml) was refluxed for 5 h, washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give **15** as crystals (0.34 g, 81.0%). Recrystallization from hexane gave colorless prisms, mp 58—59 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740. NMR δ: 1.16 (3H, s), 1.5—2.2 (8H, m), 4.67 (1H, m). *Anal.* Calcd for $C_8H_{12}O_2$: C, 68.84; H, 8.63. Found: C, 68.49; H, 8.73.

Methyl *c*-4-Hydroxy-1-methyl-*r*-1-cyclohexanecarboxylate (13)——A stirred and ice-cooled suspension of **16** (67.0 g) in Et_2O (300 ml) was treated with a solution of CH_2N_2 in Et_2O (*ca.* 3%, w/w). The usual work-up gave the title compound as a crude oil (73.0 g, quant.), which was used for the subsequent reaction without purification. An analytical sample was chromatographed on silica gel with Et_2O–hexane (1 : 2, v/v). IR ν_{max}^{neat} cm^{-1}: 3380, 1720. NMR δ: 1.15 (3H, s), 1.2—2.4 (8H, m), 2.62 (1H, br s), 3.55 (1H, m), 3.67 (3H, s). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.57; H, 9.52.

Methyl 1-Methyl-*c*-4-(2-tetrahydropyranyloxy)-*r*-1-cyclohexanecarboxylate——A mixture of methyl *c*-4-hydroxy-1-methyl-*r*-1-cyclohexanecarboxylate (72.0 g), 3,4-dihydro-α-pyran (45.7 g), *p*-TsOH (1.5 g) and Et_2O (700 ml) was stirred at room temperature for 2 h, allowed to stand overnight, then washed with H_2O, dried ($MgSO_4$) and concentrated to give the title compound as a crude oil (107 g, quant.), which was used for the subsequent reaction without purification. An analytical sample was chromatographed on silica gel with Et_2O–hexane (1 : 10, v/v). IR ν_{max}^{neat} cm^{-1}: 1730. NMR δ: 1.13 (3H, s), 1.2—2.3 (14H, m), 3.3—4.0 (3H, m), 3.66 (3H, s), 4.68 (1H, br s). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.99; H, 9.62.

1-Methyl-*c*-4-(2-tetrahydropyranyloxy)-*r*-1-cyclohexanemethanol (17)——A solution of 1-methyl-*c*-4-(2-tetrahydropyranyloxy)-*r*-1-cyclohexanecarboxylate (106 g) in Et_2O (300 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (11.4 g) in Et_2O (1 l). The mixture was stirred at room temperature for 1 h and the usual work-up gave **17** as an oil (72.6 g, 76.9%), bp 128—130 °C/0.2 mmHg. IR ν_{max}^{neat} cm^{-1}: 3400. NMR δ: 0.93 (3H, s), 1.2—2.0 (14H, m), 2.30 (1H, br s), 3.4—4.0 (5H, m), 4.78 (1H, br s). *Anal.* Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.18; H, 10.77.

4-(*c*-4-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)nitrobenzene——A mixture of **17** (72.0 g), *p*-chloronitrobenzene (48.2 g) and DMSO (700 ml) was treated with 60% NaH in oil (13.9 g) below 40 °C. The mixture was stirred at 30 °C for 3 h, poured into H_2O and extracted with Et_2O. The usual work-up of the extract gave an oily residue. The oil was dissolved in MeOH (500 ml), then 2 N HCl (500 ml) was added, and the mixture was stirred at room temperature for 1 h, diluted with H_2O and extracted with Et_2O. The usual work-up of the Et_2O extract gave the title compound as crystals (54.7 g, 67.4%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 99—100 °C. IR ν_{max}^{Nujol} cm^{-1}: 3550, 1585, 1335. NMR δ: 1.05 (3H, s), 1.1—2.0 (8H, m), 3.6—3.9 (1H, m), 3.83 (2H, s), 6.97 (2H, d, J=9), 8.20 (2H, d, J=9). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.73; H, 7.21; N, 5.54.

Methyl 2-Bromo-3-[4-(*c*-4-hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)phenyl]propionate——A mixture of 4-(*c*-4-hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)nitrobenzene (54.0 g), 10% Pd–C (50% wet, 5.0 g) and MeOH (500 ml) was hydrogenated at room temperature and 1 atm. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in acetone (500 ml), then 47% HBr aq. solution (105 g) and a

solution of $NaNO_2$ (15.5 g) in H_2O (30 ml) were added dropwise to the stirred and ice-cooled solution below 5 °C. The whole was stirred at 5 °C for 30 min, then methyl acrylate (103 g) was added thereto and the temperature was raised to 35 °C. Cu_2O (1.0 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The usual work-up gave the title compound as a crude oil (78.0 g, 99.2%), which was used for the subsequent reaction without purification. Purification by column chromatography on silica gel with AcOEt–cyclohexane (1 : 3, v/v) gave the title compound as crystals, mp 63—64 °C (from Et_2O–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3380, 1740. NMR δ: 1.01 (3H, s), 1.1—1.9 (8H, m), 3.12 (1H, q, J=14 and 7), 3.39 (1H, q, J=14 and 7), 3.70 (5H, s), 3.75 (1H, m), 4.33 (1H, t, J=7), 6.80 (2H, d, J=9), 7.09 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{25}BrO_4$: C, 56.11; H, 6.54. Found: C, 56.12; H, 6.57.

5-[4-(*c*-4-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2-imino-4-thiazolidinone——A mixture of methyl 2-bromo-3-[4-(*c*-4-hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)phenyl]propionate (76.0 g), thiourea (15.0 g), NaOAc (16.2 g) and EtOH (500 ml) was stirred under reflux for 3 h and concentrated *in vacuo*. The residue was neutralized with $NaHCO_3$ aq. solution and Et_2O (200 ml)–hexane (200 ml) was added thereto. The mixture was stirred at room temperature for 30 min and the crystals (47.5 g, 69.2%) were filtered off. Recrystallization from EtOH gave colorless crystals, mp 215—217 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3230, 1685. NMR (d_6-DMSO) δ: 0.96 (3H, s), 1.1—1.9 (8H, m), 2.80 (1H, q, J=14 and 9), 3.30 (1H, q, J=14 and 4), 3.70 (2H, s), 4.26 (1H, m), 4.37 (1H, q, J=9 and 4), 6.82 (2H, d, J=9), 7.12 (2H, d, J=9), 8.73 (2H, br s). *Anal.* Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; N, 8.04. Found: C, 62.02; H, 7.02; N, 7.98.

5-[4-(*c*-4-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (3, *cis*-4′-ol)——A mixture of 5-[4-(*c*-4-hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2-imino-4-thiazolidinone (45.0 g), 2 N HCl (300 ml) and EtOH (300 m) was refluxed for 24 h and diluted with H_2O to give **3** as crystals (40.0 g, 88.5%). Recrystallization from 75% EtOH gave colorless prisms, mp 120—121 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3180, 1745, 1685. NMR δ: 1.01 (3H, s), 1.1—1.9 (8H, m), 3.02 (1H, q, J=14 and 9), 3.43 (1H, q, J=14 and 4), 3.72 (2H, s), 3.80 (1H, m), 4.45 (1H, q, J=9 and 4), 6.86 (2H, d, J=9), 7.15 (2H, d, J=9), 8.80 (1H, br s). *Anal.* Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 61.73; H, 6.65; N, 4.10.

Oxymercuration-reduction of Methyl 1-Methyl-3-cyclohexenecarboxylate (18)——A solution of **18**[9] (48.4 g) in THF (50 ml) was added to a stirred solution of $Hg(OAc)_2$ (100 g) in THF (300 ml)–H_2O (300 ml). The mixture was stirred at room temperature for 30 min, then 3 N NaOH (300 ml) and a solution of $NaBH_4$ (8.0 g) in 3 N NaOH (300 ml) were added dropwise at room temperature and Hg isolated was removed by filtration. The filtrate was extracted with Et_2O. The usual work-up of the extract gave **14** as an oil (25.0 g, 46.2%), bp 90—93 °C/0.5 mmHg. IR ν_{max}^{neat} cm^{-1}: 3400, 1725. NMR δ: 1.20 (3H, s), 1.4—2.0 (8H, m), 3.68 (3H, s), 3.6—3.9 (1H, m). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.55; H, 9.51. GLC analysis of the corresponding Me_3Si ether at 95 °C showed one peak. The aqueous layer of the above extract was acidified with conc. HCl and extracted with AcOEt. The usual work-up of the AcOEt extract gave **19** as crystals (11.7 g, 23.5%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 138—139 °C. IR ν_{max}^{Nujol} cm^{-1}: 3420, 1700. NMR (d_6-DMSO) δ: 1.11 (3H, s), 1.3—1.8 (8H, m), 3.57 (1H, m). *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 61.11; H, 8.67.

The following compounds were prepared in the same manner as described for the *cis*-4-hydroxy compounds.

1-Methyl-*t*-4-(2-tetrahydropyranyloxy)-*r*-1-cyclohexanemethanol (20)——Yield 92.5% (based on **14**). bp 130—135 °C/0.4 mmHg. IR ν_{max}^{neat} cm^{-1}: 3420. NMR δ: 0.92 (3H, s), 1.1—2.0 (15H, m), 3.30 (2H, br s), 3.4—3.7 (2H, m), 3.75—4.05 (1H, m), 4.71 (1H, m). *Anal.* Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.27; H, 10.64.

4-(*t*-4-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)nitrobenzene——Yield 67.2%. mp 91—92 °C (from Et_2O–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3260, 1590, 1335. NMR δ: 1.09 (3H, s), 1.4—2.1 (9H, m), 3.5—3.8 (1H, m), 3.72 (2H, s), 6.97 (2H, d, J=9), 8.26 (2H, d, J=9). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.28; H, 7.05; N, 5.18.

Methyl 2-Bromo-3-[4-(*t*-4-hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)phenyl]propionate——A crude oil was obtained in 94.9% yield and was used for the subsequent reaction without purification. Purification by column chromatography on silica gel with AcOEt–cyclohexane (1 : 3, v/v) gave the title compound as crystals, mp 76—77 °C (from Et_2O–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1735. NMR δ: 1.05 (3H, s), 1.3—1.9 (8H, m), 3.07 (1H, q, J=14 and 7), 3.35 (1H, q, J=14 and 7), 3.52 (2H, s), 3.65 (3H, s), 4.28 (1H, t, J=7), 6.73 (2H, d, J=9), 7.03 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{25}BrO_4$: C, 56.11; H, 6.54. Found: C, 55.81; H, 6.52.

5-[4-(*t*-4-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2-imino-4-thiazolidinone Hemihydrate——Yield 60.5% (based on the crude oil of the bromoester). mp 259—260 °C (dec.) (from EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3220, 1675. NMR (d_6-DMSO) δ: 0.98 (3H, s), 1.2—1.8 (8H, m), 2.78 (1H, q, J=14 and 10), 3.29 (1H, q, J=14 and 4), 3.5 (1H, m), 3.57 (2H, s), 4.3 (1H, br), 4.45 (1H, q, J=10 and 4), 6.78 (2H, d, J=9), 8.60 (1H, br s), 8.82 (1H, br s). *Anal.* Calcd for $C_{18}H_{24}N_2O_3S \cdot 1/2H_2O$: C, 60.48; H, 7.05; N, 7.84. Found: C, 60.65; H, 6.95; N, 7.81.

5-[4-(*t*-4-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (4, *trans*-4′-ol)——Yield 98.6%. mp 171—172 °C (from 75% EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3480, 3130, 1740, 1685. NMR δ: 1.06 (3H, s), 1.2—2.0 (8H, m), 3.08 (1H, q, J=14 and 9), 3.44 (1H, q, J=14 and 4), 3.59 (2H, s), 3.7 (1H, m), 4.49 (1H, q, J=9 and 4), 6.83 (2H, d, J=9), 7.15 (2H, d, J=9), 8.45 (1H, br s). *Anal.* Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 61.68; H, 6.81; N, 4.01.

Hydroxybromination of 18——NBS (63.4 g) was added in small portions to a stirred mixture of **18** (50.0 g), H_2O (40 ml) and DMSO (400 ml) at 20 °C. The mixture was stirred at room temperature for 2 h, diluted with H_2O and extracted with Et_2O. The usual work-up of the extract gave **21** as an oil (81.5 g, quant.). The crude oil was used for the subsequent reaction without purification. IR ν_{max}^{neat} cm^{-1}: 3430. NMR δ: 1.27 (3H, s), 1.5—2.5 (7H, m), 3.10 (1H, s), 3.73 (3H, s), 3.8—4.2 (1H, m).

Methyl 3,4-Epoxy-1-methylcyclohexanecarboxylate (23)——a) Powdered NaOH (80.0 g) was added in small portions to a stirred solution of **21** (81.5 g) in C_6H_6 (500 ml). The mixture was stirred at room temperature for 3 h and the insoluble solid was removed by filtration. The filtrate was washed with brine, dried ($MgSO_4$) and distilled to give **23** (59.5 g, 80.6%), bp 59—60 °C/0.1 mmHg. *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.36; H, 8.16. GLC analysis at 100 °C showed two peaks in a ratio of 3 : 1.

b) A solution of *m*-chloroperbenzoic acid (70%, 11.8 g) in $CHCl_3$ (100 ml) was added dropwise to a stirred and ice-cooled mixture of **18** (6.17 g), $NaHCO_3$ (4.2 g) and $CHCl_3$ (100 ml). The whole was stirred with ice-cooling for 1 h and the usual work-up gave **23** (6.8 g, quant.). GLC analysis at 100 °C showed two peaks in a ratio of 3 : 1.

Methyl 1-Methyl-3-oxo-4-cyclohexenecarboxylate (22)——a) A solution of di-*tert*-butylchromate[prepared from CrO_3 (18.0 g)] in CCl_4 was added dropwise to a stirred solution of **18** (11.0 g), Ac_2O (18 ml), AcOH (13 ml) in C_6H_6 (200 ml) under reflux. The whole was refluxed for 25 h, then cooled and a solution of oxalic acid (15.0 g) in H_2O (200 ml) was added thereto. The organic layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil. The oil was chromatographed on silica gel (150 g) with Et_2O–hexane (2 : 3, v/v) to give **22** as an oil (2.3 g, 19.3%). IR ν_{max}^{neat} cm^{-1}: 1730, 1680. NMR δ: 1.30 (3H, s), 2.0—3.0 (4H, m), 3.60 (3H, s), 5.88 (1H, dt, J = 10 and 1.5), 6.71 (1H, dt, J = 10 and 5). *Anal.* Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.15.

b) Jones reagent (180 ml) was added dropwise to a stirred and ice-cooled solution of **21** (77.0 g) in acetone (500 ml). The mixture was stirred at room temperature for 30 min and MeOH (40 ml) was added thereto. The whole was concentrated, and the residue was diluted with H_2O and extracted with Et_2O. The usual work-up of the Et_2O extract gave the bromoketone as an oil (50.7 g, 66.4%), bp 127—133 °C/2 mmHg. A mixture of the bromoketone (50.0 g), $LiBr \cdot H_2O$ (23.1 g), Li_2CO_3 (36.9 g) and DMF (400 ml) was stirred at 120 °C for 4 h, poured into ice (1 kg)–AcOH (30 ml) and extracted with C_6H_6. The usual work-up of the C_6H_6 extract gave an oily residue which was purified by column chromatography on silica gel (500 g) using Et_2O–hexane (2 : 3, v/v) as an eluent to afford **22** (11.3 g, 33.6%).

Methyl 1-Methyl-3-oxocyclohexanecarboxylate (24)——a) Jones reagent (40 ml) was added dropwise to a stirred and ice-cooled solution of methyl *t*-3-hydroxy-1-methyl-*r*-1-cyclohexanecarboxylate (22.0 g) in acetone (200 ml). The mixture was stirred at room temperature for 30 min an MeOH (10 ml) was added thereto. The whole was concentrated, and the residue was diluted with H_2O and extracted with Et_2O. The usual work-up of the Et_2O extract gave **24** as an oil (18.5 g, 85.3%), bp 87—89 °C/0.3 mmHg. IR ν_{max}^{neat} cm^{-1}: 1725 (br). NMR δ: 1.27 (3H, s), 1.6—2.9 (8H, m), 3.71 (3H, s). *Anal.* Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.38; H, 8.03.

b) A mixture of **22** (10.0 g), 10% Pd–C (50% wet, 0.5 g) and AcOEt (100 ml) was hydrogenated at room temperature and 1 atm. The catalyst was removed by filtration, and the filtrate was concentrated to give **24** (10.1 g, quant.).

c) A mixture of **23** (39.0 g), PtO_2 (5.0 g) and AcOH (300 ml) was hydrogenated at 50 °C and 1 atm. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to leave an oil. The oil was dissolved in acetone (300 ml). Jones reagent (85 ml) was added dropwise to the stirred and ice-cooled solution. The whole was stirred at room temperature for 30 min and MeOH (20 ml) was added thereto. The usual work-up gave an oil, which was chromatographed on silica gel (400 g) with AcOEt–cyclohexane (1 : 4, v/v) to afford **24** (10.5 g, 26.9%).

The following compounds were prepared in the same manner as described for the 4-oxo compounds.

Methyl 3,3-Ethylenedioxy-1-methylcyclohexanemethanol (25)——Yield 77.9% (based on **24**). bp 103—105 °C/0.5 mmHg. IR ν_{max}^{neat} cm^{-1}: 3420. NMR δ: 0.93 (3H, s), 1.3—2.0 (8H, m), 2.83 (1H, br), 3.33 (2H, br), 3.87 (4H, s). *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.14; H, 9.88.

4-(3,3-Ethylenedioxy-1-methylcyclohexylmethoxy)nitrobenzene——Yield 59.2% (based on **25**) [oil, purified by column chromatography on silica gel with Et_2O–hexane (1 : 10, v/v)]. IR ν_{max}^{neat} cm^{-1}: 1585, 1335. NMR δ: 1.12 (3H, s), 1.2—1.8 (8H, m), 3.92 (4H, s), 7.03 (2H, d, J = 9), 8.26 (2H, d, J = 9). *Anal.* Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.92; H, 6.97; N, 4.56.

Methyl 2-Chloro-3-[4-(1-methyl-3-oxocyclohexylmethoxy)phenyl]propionate——Yield 70.3% [based on 4-(3,3-ethylenedioxy-1-methylcyclohexylmethoxy)nitrobenzene] (oil). IR ν_{max}^{neat} cm^{-1}: 1745, 1705. NMR δ: 1.04 (3H, s), 1.5—2.6 (8H, m), 3.04 (1H, q, J = 14 and 7), 3.34 (1H, q, J = 14 and 7), 3.66 (2H, s), 3.71 (3H, s), 4.40 (1H, t, J = 7), 6.82 (2H, d, J = 9), 7.18 (2H, d, J = 9). *Anal.* Calcd for $C_{18}H_{23}ClO_4$: C, 63.81; H, 6.84. Found: C, 63.50; H, 6.86.

5-[4-(1-Methyl-3-oxocyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (5, 3′-oxo)——Yield 74.0% {based on methyl 2-chloro-3-[4-(1-methyl-3-oxocyclohexylmethoxy)phenyl]propionate}. mp 170—171 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3130, 3030, 1750, 1700. NMR δ: 1.04 (3H, s), 1.6—2.2 (4H, m), 2.2—2.5 (4H, m), 3.06 (1H, q, J = 14 and 9), 3.45 (1H, q, J = 14 and 5), 3.66 (2H, s), 4.47 (1H, q, J = 9 and 5), 6.83 (2H, d, J = 9), 7.16 (2H, d, J = 9), 8.9 (1H, br). *Anal.* Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.26; H, 6.16; N, 4.08.

Lactonization of 26——Conc. H_2SO_4 (100 ml) and $CHCl_3$ (100 ml) were added in one portion to a stirred and ice-

cooled solution of **26**[12] (47.0 g) in $CHCl_3$ (200 ml). The mixture was stirred at 0 °C for 15 min and extracted with $CHCl_3$. The usual work-up of the $CHCl_3$ extract gave an oil, which was chromatographed on silica gel (400 g) with Et_2O–hexane (1 : 4, v/v). The first part of the eluate gave **27** as crystals (28.0 g, 59.6%). Recrystallization from hexane gave colorless rods, mp 38—39 °C. IR ν_{max}^{Nujol} cm^{-1}: 1785. NMR δ: 1.18 (3H, s), 1.3—2.3 (8H, m), 4.75 (1H, m). *Anal.* Calcd for $C_8H_{12}O_2$: C, 68.84; H, 8.63. Found: C, 68.44; H, 8.75. Further elution gave **15** as crystals (5.3 g, 11.3%), mp 58—59 °C (from hexane).

The following compounds were prepared in the same manner as described for the *cis*-4-hydroxy compounds.

c-3-Hydroxy-1-methyl-r-1-cyclohexanecarboxylic Acid (28)——Yield 80.6% (based on **27**). mp 131—132 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3430, 1690. NMR (d_6-DMSO) δ: 1.09 (3H, s), 1.3—1.9 (8H, m), 3.57 (1H, m). *Anal.* Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.93; H, 9.02.

1-Methyl-c-3-(2-tetrahydropyranyloxy)-r-1-cyclohexanemethanol (29)——Yield 81.9% (based on **28**). bp 130—132 °C/0.2 mmHg. IR ν_{max}^{neat} cm^{-1}: 3430. NMR δ: 0.90 (3H, s), 1.1—2.0 (14H, m), 2.07 (1H, br), 3.20 (2H, s), 3.3—3.6 (1H, m), 3.6—4.1 (2H, m), 4.7 (1H, br s). *Anal.* Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.11; H, 10.70.

4-(c-3-Hydroxy-1-methyl-r-1-cyclohexylmethoxy)nitrobenzene——Yield 68.8% (based on **29**). mp 120—121 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3525, 1585, 1325. NMR δ: 1.05 (3H, s), 1.1—2.1 (8H, m), 3.6—4.0 (1H, m), 3.72 (2H, s), 6.94 (2H, d, J=9), 8.19 (2H, d, J=9). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.40; H, 6.92; N, 5.20.

Methyl 2-Bromo-3-[4-(c-3-hydroxy-1-methyl-r-1-cyclohexylmethoxy)phenyl]propionate——A crude oil was obtained in 93.3% yield and was used for the subsequent reaction without purification. Purification by column chromatography on silica gel with AcOEt–cyclohexane (1 : 3, v/v) gave the title compound as crystals, mp 78—79 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3370, 1740. NMR δ: 1.01 (3H, s), 1.1—2.1 (8H, m), 3.11 (1H, q, J=14 and 7), 3.38 (1H, q, J=14 and 7), 3.57 (2H, s), 3.68 (3H, s), 3.80 (1H, m), 4.32 (1H, t, J=7), 6.77 (2H, d, J=9), 7.07 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{25}BrO_4$: C, 56.11; H, 6.54. Found: C, 56.16; H, 6.64.

5-[4-(c-3-Hydroxy-1-methyl-r-1-cyclohexylmethoxy)benzyl]-2-imino-4-thiazolidinone——Yield 55.9% (based on the crude oil of the bromoester). mp 235—237 °C (dec.) (from AcOEt–MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3240, 1675. NMR (d_6-DMSO) δ: 0.97 (3H, s), 1.1—1.9 (8H, m), 2.80 (1H, q, J=14 and 9), 3.31 (1H, q, J=14 and 4), 3.57 (2H, s), 3.7 (1H, m), 4.32 (1H, d, J=5), 4.47 (1H, q, J=9 and 4), 6.78 (2H, d, J=9), 7.10 (2H, d, J=9), 8.60 (1H, br s), 8.83 (1H, br s). *Anal.* Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; N, 8.04. Found: C, 61.70; H, 7.22; N, 8.05.

5-[4-(c-3-Hydroxy-1-methyl-r-1-cyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (6, *cis*-3′-ol)——Yield 63.8%. mp 130—131 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3190, 1750, 1685, 1670. NMR δ: 1.03 (3H, s), 1.1—2.2 (8H, m), 3.04 (1H, q, J=14 and 9), 3.42 (1H, q, J=14 and 5), 3.60 (2H, s), 3.6—4.0 (1H, m), 4.45 (1H, q, J=9 and 5), 6.82 (2H, d, J=9), 7.12 (2H, d, J=9), 9.25 (1H, br s). *Anal.* Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 61.92; H, 6.55; N, 4.15.

Methyl 1-Methyl-t-3-(2-tetrahydropyranyloxy)-r-1-cyclohexanecarboxylate (31)——A solution of *n*-BuLi in hexane (1.6 M, 229 ml) was added to a solution of diisopropylamine (37.6 g) in anhydrous THF (800 ml) at −65 °C under an N_2 atmosphere, and the mixture was stirred for 30 min. Methyl 3-(2-tetrahydropyranyloxy)-cyclohexanecarboxylate (**30**) (60.0 g) dissolved in anhydrous THF (200 ml) was added at a rate such that the reaction temperature was kept below −60 °C. The resultant clear, almost colorless solution was stirred at dry ice temperature for 1 h, and CH_3I (52.7 g) was added. Stirring at −70 °C was continued for an additional 2 h, then the reaction mixture was warmed to room temperature and poured into ice-H_2O containing Et_2O (1 l). The layers were separated, and the aqueous portion was extracted with Et_2O. The combined organic layer was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was distilled to afford **31** as a pure oil (61.0 g, 95.9%), bp 120—125 °C/0.3 mmHg. IR ν_{max}^{neat} cm^{-1}: 1730. NMR δ: 1.18 (3H, s), 1.1—2.1 (14H, m), 3.65 (3H, s), 3.3—4.1 (3H, m), 4.70 (1H, br s). *Anal.* Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.33; H, 9.66. This compound was converted to methyl *t*-3-hydroxy-1-methyl-*r*-1-cyclohexanecarboxylate by the usual acid treatment in 91.3% yield, bp 110—113 °C/0.5 mmHg. IR ν_{max}^{neat} cm^{-1}: 3370, 1730. NMR δ: 1.18 (3H, s), 1.1—2.2 (8H, m), 3.40 (1H, br), 3.65 (3H, s). *Anal.* Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.45; H, 9.50. GLC analysis of the corresponding Me_3Si ether at 95 °C showed one peak.

The following compounds were prepared in the same manner as described for the *cis*-4-hydroxy compounds.

1-Methyl-t-3-(2-tetrahydropyranyloxy)-r-1-cyclohexanemethanol (32)——Yield 92.4%. bp 130—133 °C/0.1 mmHg. IR ν_{max}^{neat} cm^{-1}: 3400. NMR δ: 0.96 (3H, s), 1.1—2.0 (14H, m), 3.2—4.1 (6H, m), 4.70 (1H, br s). *Anal.* Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.19; H, 11.26.

4-(t-3-Hydroxy-1-methyl-r-1-cyclohexylmethoxy)nitrobenzene——Yield 75.8% (based on **32**). mp 114—115 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3525, 1585, 1335. NMR δ: 1.09 (3H, s), 1.1—2.2 (8H, m), 3.7 (1H, m), 3.79 (2H, m), 6.93 (2H, d, J=9), 8.18 (2H, d, J=9). *Anal.* Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.48; H, 7.06; N, 5.32.

Methyl 2-Bromo-3-[4-(t-3-hydroxy-1-methyl-r-1-cyclohexylmethoxy)phenyl]propionate——A crude oil was obtained in 92.6% yield and was used for the subsequent reaction without purification. Purification by column chromatography on silica gel with AcOEt–cyclohexane (1 : 3, v/v) gave the title compound as an oil. IR ν_{max}^{Nujol} cm^{-1}: 3370, 1740. NMR δ: 1.07 (3H, s), 1.1—2.2 (8H, m), 3.13 (1H, q, J=14 and 7), 3.40 (1H, q, J=14 and 7), 3.66 (2H, s),

3.70 (3H, s), 3.75 (1H, m), 4.34 (1H, t, J=7), 6.79 (2H, d, J=9), 7.08 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{25}BrO_4$: C, 56.11; H, 6.54. Found: C, 56.00; H, 6.69.

5-[4-(*t*-3-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2-imino-4-thiazolidinone——Yield 59.1% (based on the crude oil of the bromoester). mp 219—220 °C (from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3240, 1675. NMR (d_6-DMSO) δ: 1.02 (3H, s), 1.1—2.0 (8H, m), 2.82 (1H, q, J=14 and 10), 3.31 (1H, q, J=14 and 4), 3.5 (1H, m), 3.68 (2H, s), 4.33 (1H, d, J=5), 4.47 (1H, q, J=10 and 4), 6.81 (2H, d, J=9), 7.12 (2H, d, J=9), 8.62 (1H, br s), 8.85 (1H, br s). *Anal.* Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; N, 8.04. Found: C, 61.86; H, 6.85; N, 7.87.

5-[4-(*t*-3-Hydroxy-1-methyl-*r*-1-cyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (7, *trans*-3′-ol)——Yield 94.3%. mp 143—145 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3430, 3130, 1735, 1685. NMR δ: 1.07 (3H, s), 1.1—2.2 (8H, m), 3.04 (1H, q, J=14 and 9), 3.42 (1H, q, J=14 and 4), 3.67 (2H, s), 3.7—4.0 (1H, m), 4.45 (1H, q, J=9 and 4), 6.82 (2H, d, J=9), 7.12 (2H, d, J=9), 8.70 (1H, br s). *Anal.* Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 61.95; H, 6.47; N, 4.07.

The following compounds were prepared in the same manner as described for the 4-oxo compounds.

2,2-Ethylenedioxy-1-methylcyclohexanemethanol (34)——Yield 79.6% (based on **33**[13]). bp 105—108 °C/1 mmHg. IR ν_{max}^{neat} cm^{-1}: 3400. NMR δ: 1.0 (3H, s), 1.6 (8H, m), 3.15 (1H, d, J=6), 3.65 (2H, d, J=6), 4.07 (4H, s). *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.49; H, 9.94.

4-(2,2-Ethylenedioxy-1-methylcyclohexylmethoxy)nitrobenzene——Yield 77.4%. mp 73—74 °C (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1590, 1335. NMR δ: 1.15 (3H, s), 1.62 (8H, m), 3.97 (4H, s), 4.06 (2H, s), 7.0 (2H, d, J=9), 8.23 (2H, d, J=9). *Anal.* Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.63; H, 6.95; N, 4.95.

Methyl 2-Chloro-3-[4-(1-methyl-2-oxocyclohexylmethoxy)phenyl]propionate——Yield 57.5% (oil). IR ν_{max}^{neat} cm^{-1}: 1740, 1705. NMR δ: 1.23 (3H, s), 1.85 (6H, m), 2.45 (2H, m), 3.07 (1H, q, J=14 and 7), 3.37 (1H, q, J=14 and 7), 3.73 (3H, s), 3.99 (2H, s), 4.43 (1H, t, J=7), 6.90 (2H, d, J=9), 7.19 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{23}ClO_4$: C, 63.81; H, 6.84. Found: C, 63.69; H, 6.97.

5-[4-(1-Methyl-2-oxocyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (8, 2′-oxo)——Yield 77.9% {based on methyl 2-chloro-3-[4-(1-methyl-2-oxocyclohexylmethoxy)phenyl]propionate}. mp 123—125 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1745, 1705, 1680. NMR δ: 1.23 (3H, s), 1.85 (6H, m), 2.3—2.6 (2H, m), 3.03 (1H, q, J=14 and 9), 3.45 (1H, q, J=14 and 5), 3.96 (2H, s), 4.46 (1H, q, J=9 and 5), 6.85 (2H, d, J=9), 7.15 (2H, d, J=9), 9.20 (1H, br s). *Anal.* Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.44; H, 5.99; N, 4.30.

5-[4-(2-Hydroxy-1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione (9, 2′-ol)——$NaBH_4$ (0.757 g) was added to a stirred and ice-cooled solution of **8** (5.2 g) in MeOH (50 ml). The mixture was stirred at room temperature for 1 h, then poured into H_2O and extracted with AcOEt. The usual work-up of the AcOEt extract gave an oily residue. Purification by column chromatography on silica gel (100 g) with C_6H_6–acetone (10:1, v/v) gave **9** as an amorphous solid (4.2 g, 80.0%), mp 101—103 °C. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3220, 1750, 1680. NMR δ: 1.03 (2H, s), 1.12 (1H, s), 1.2—2.0 (8H, m), 3.0 (1H, q, J=14 and 9), 3.42 (1H, q, J=14 and 4), 3.71 (0.7H, s), 3.77 (1.3H, s), 3.8 (1H, m), 4.38 (1H, q, J=9 and 4), 6.87 (2H, d, J=9), 7.12 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01. Found: C, 62.02; H, 6.34; N, 4.20.

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References and Notes

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