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Potential Antiinflammatory Agents. IV.[1] Stereoselective Synthesis of 6-Chloro-5-(3′- and 4′-hydroxycyclohexyl)indan-1-carboxylic Acids related to Metabolites of 6-Chloro-5-cyclohexylindan-1-carboxylic Acid (TAI-284)[2]

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In the course of synthetic study of metabolites of a new potent antiinflammatory agent, 6-chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284), 5-(*cis*- and *trans*-3′-hydroxycyclohexyl)indan-1-carboxylic acids (**25** and **26**) and 5-(*cis*- and *trans*-4′-hydroxycyclohexyl)indan-1-carboxylic acids (**17** and **16**) were stereoselectively prepared by sodium borohydride reduction (equatorial alcohol formation) and catalytic hydrogenation (axial alcohol formation) of the corresponding 3′-oxo and 4′-oxo compounds (**24** and **15**), respectively. Chlorination of **25**, **26**, **17** and **16** with molecular chlorine in acetonitrile gave their 6-chloro derivatives (**27**, **28**, **21** and **20**), which were correlated with metabolites of TAI-284. Of these indans, 3′-hydroxy compounds (**25**—**28**) were prepared as a pair of racemic diastereoisomers.

In the previous paper,[4] we reported the synthesis of 6-chloro-5-cyclohexylindan-1-carboxylic acid (TAI-284), which exhibited remarkable antiinflammatory, analgetic and antipyretic activities.[5] The metabolism of this compound in rats was studied by Tanayama[6] and Kanai,[7] who isolated five metabolites, I, IIa, IIb, III and IV, from the perfusate of the isolated liver perfusion. Structures of these metabolites were assigned 4′-oxo-, *cis*-4′-hydroxy-, *cis*-3′-hydroxy-, *trans*-4′-hydroxy- and *cis*-3′-hydroxy-6-chloro-5-cyclohexylindan-1-carboxylic acids, respectively, by means of mass and nuclear magnetic resonance (NMR) spectroscopy and confirmed by direct comparison with authentic samples prepared by these authors (Fig. 1). Of these metabolites, IIb and IV, both of which have *cis*-3′-hydroxy structures, were diastereoisomeric with each other. The present paper describes the stereoselective synthesis of 3′- and 4′-hydroxylated 6-chloro-5-cyclohexylindan-1-carboxylic acids related to the metabolites of TAI-284.

Two routes were considered for the preparation of 5-(4′-hydroxycyclohexyl)indan-1-carboxylic acids. First a route *via* the cyclization of 4-(4′-hydroxycyclohexyl)phenylsuccinic acids was attempted by essentially the same method as described in the preparation of TAI-284 as previously reported.[4] Thus 4-(*trans*-4′-hydroxycyclohexyl)phenylsuccinic acid (**4**) was synthesized from *trans*-4′-acetoxycyclohexylbenzene[8] (**1**) in three steps, as shown in Chart 1.

1) Part III: S. Noguchi, M. Obayashi, S. Kishimoto and M. Imanishi, *Chem. Pharm. Bull.* (Tokyo), **22**, 537 (1974).
2) A part of this work was presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973.
3) Location: *Juso-Honmachi, Yodogawa-ku, Osaka.*
4) S. Noguchi, S. Kishimoto, I. Minamida and M. Obayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 529 (1974).
5) K. Kawai, S. Kuzuna, S. Morimoto, H. Ishii and N. Matsumoto, *Jap. J. Pharmacol.*, **21**, 621 (1971); S. Noguchi, S. Kishimoto, I. Minamida, M. Obayashi and K. Kawakita, *Chem. Pharm. Bull.* (Tokyo), **19**, 646 (1971).
6) S. Tanayama, E. Tsuchida and Z. Suzuoki, *Xenobiotica*, **3**, 643 (1973).
7) Y. Kanai, T. Kobayashi and S. Tanayama, *Xenobiotica*, **3**, 657 (1973).
8) Merck & Co., Inc., Dutch Patent 6608098 (1966) [*C.A.*, **67**, 2053 (1967)].

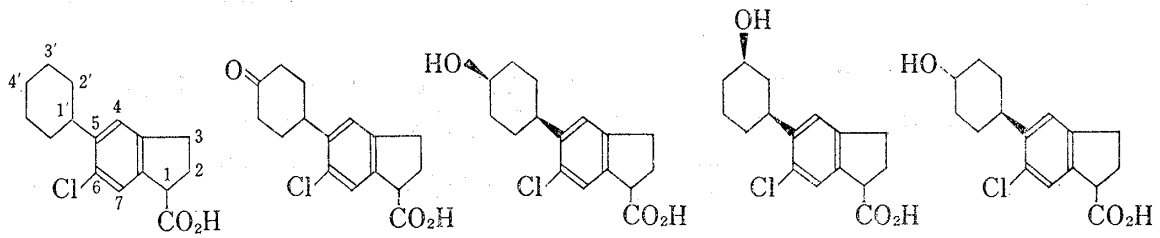


Fig. 1. Structures of TAI-284 and Its Metabolites in Rats

Heating of **4** in acetic anhydride gave its acid anhydride (**5**). When the anhydride (**5**) was treated with aluminum chloride in dichloromethane for cyclization, the thin-layer chromatography (TLC) of the reaction mixture showed the formation of many products and the expected indanone (**6**) could not be isolated.

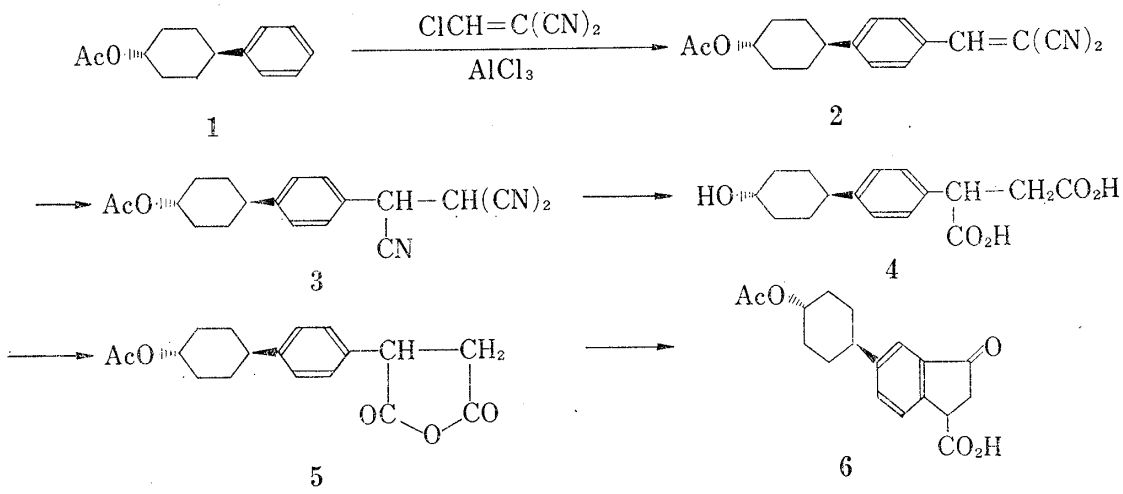


Chart 1

In the second attempt, 4-(4′-oxocyclohexyl)phenylsuccinic acid (**12a**) was adopted as a key intermediate. **12a** was prepared from 4-phenylcyclohexanone (**7a**) as shown in Chart 2. Treatment of **7a** with chloromethyl methyl ether in the presence of titanium tetrachloride gave 4-(4′-oxocyclohexyl)benzylchloride (**8a**) in about 40% yield. In contrast, *cis*- or *trans*-4′-acetoxycyclohexylbenzene did not undergo chloromethylation under these conditions. After the protection of the carbonyl group of **8a** as the ethylene acetal derivative, the resulting benzylchloride (**9a**) was treated with sodium cyanide to give the benzylcyanide (**10a**), which was converted to **12a** in the procedures previously reported in the preparation of 4-cyclohexylphenylsuccinic acid.[4]

Treatment of the anhydride (**13**) of **12a** with an excess of aluminum chloride in dichloromethane afforded the cyclized product (**14**), mp 170—173°, in 89% yield. Catalytic hydrogenation of **14** with 5% palladium charcoal gave 5-(4′-oxocyclohexyl)indan-1-carboxylic acid (**15**), mp 126—128°, in 87% yield. Attempts to introduce a chlorine substituent at C-6 of **15** by the use of molecular chlorine in acetonitrile gave a mixture of polychlorinated compounds. This shows a sharp contrast to the previous finding that 5-cyclohexylindan-1-carboxylic acid underwent selective mono-chlorination at C-6 under the similar conditions.[4] This would probably be attributed to the ready chlorination of the cyclohexane ring by the presence of

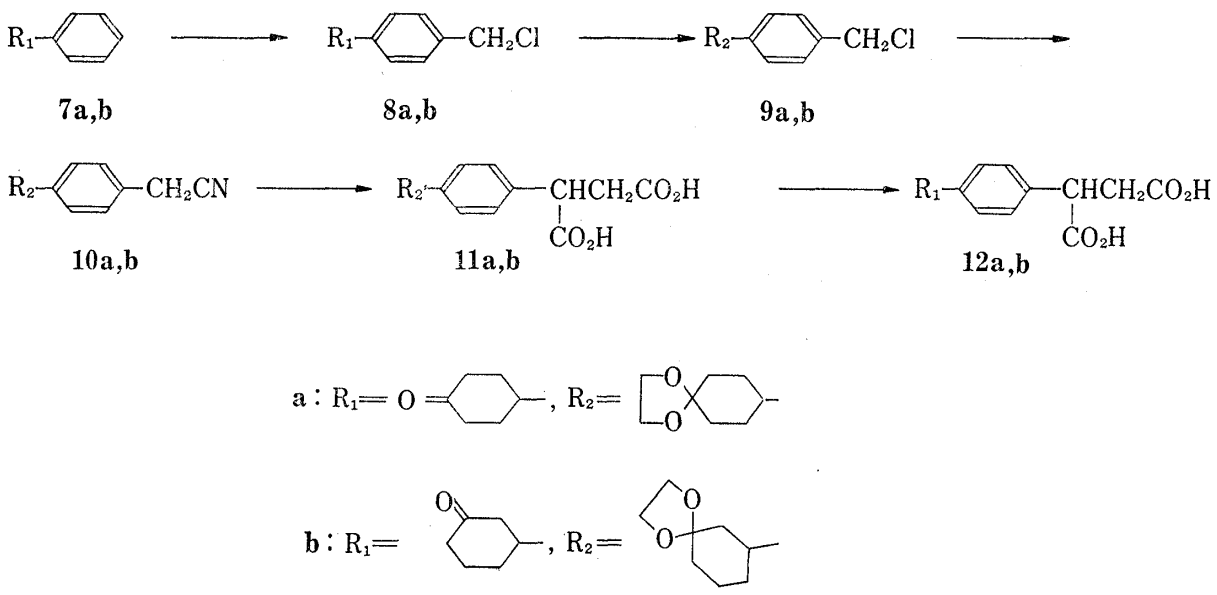


Chart 2

the 4′-carbonyl group in **15**. When aluminum chloride was used to suppress such aliphatic chlorination by the formation of a molten complex[9] with the carbonyl group, a considerable amount of 4-chloro isomer was formed along with the desired 6-chloro compound. To avoid these disadvantages, the carbonyl group was reduced to the alcohol prior to the chlorination. Generally, reduction of a relatively unhindered monosubstituted cyclohexanone with sodium borohydride produces the more stable equatorial alcohol predominantly. In contrast, catalytic hydrogenation tends to give the less stable axial hydroxy compound of the two epimeric alcohols.[10] Reduction of **15** with sodium borohydride in an alkaline solution gave the expected stable equatorial alcohol, 5-(*trans*-4′-hydroxycyclohexyl)indan-1-carboxylic acid (**16**), mp 177—179°, in 79% yield, and catalytic hydrogenation of **15** with platinum oxide in an acidic solution gave the axial alcohol, 5-(*cis*-4′-hydroxycyclohexyl)indan-1-carboxylic acid (**17**), mp 186—188°, in 64% yield. The conformation of the hydroxyl groups at C-4′ in these compounds (**16** and **17**) was confirmed on the basis of the NMR and infrared (IR) spectra of their methyl esters (**18** and **19**). In the NMR spectra, a proton at C-4′ in **18** exhibited a much broader signal at higher field (3.67 ppm) than that in **19** (4.10 ppm), indicating that the former compound has an equatorial hydroxyl at C-4′ and the latter an axial one.[11] These stereochemical features were also confirmed by the IR spectra, which exhibited absorption bands at 1070 cm^{-1} in **18** and 950 cm^{-1} in **19**, corresponding to C–O stretching for equatorial and axial hydroxyls,[12] respectively.

When two equivalents of chlorine were reacted with *trans*-4′-hydroxy compound (**16**) in acetonitrile,[4] 6-chloro-5-(*trans*-4′-hydroxycyclohexyl)indan-1-carboxylic acid (**20**), mp 188—190°, was obtained in 13.4% yield (Chart 3). In the NMR spectrum, **20** showed two singlets at 7.09 and 7.35 ppm due to the substantially uncoupled aromatic protons at C-4 and C-7, indicating that the chlorine atom was introduced into the C-6 of **16**. Similarly *cis*-4′-hydroxy compound (**17**) was chlorinated with chlorine to give the 6-chloro derivative (**21**), mp 206—208°, in 23% yield. When a large excess of chlorine was added to **16** or **17**, less polar compounds were formed. The IR spectrum of a mixture of the less polar products

9) D.E. Person, H.W. Pope, W.W. Hargrove and W.E. Stamper, *J. Org. Chem.*, **23**, 1412 (1958).
10) D.H.R. Barton, *J. Chem. Soc.*, **1953**, 1027.
11) Y. Kawazoe, Y. Sato, T. Okamoto and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963); J.I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).
12) R.N. Jones and G. Roberts, *J. Am. Chem. Soc.*, **80**, 6121 (1958).

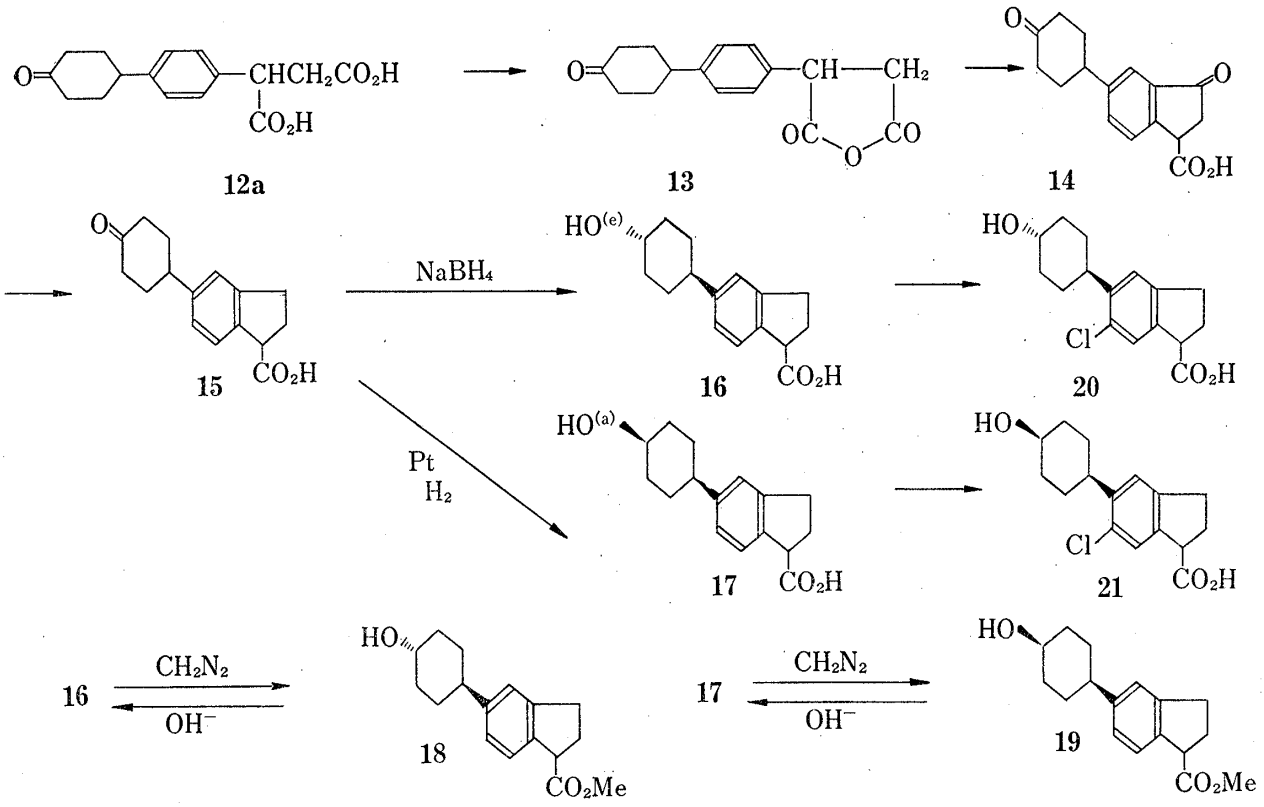


Chart 3

exhibited an absorption band at 1730 cm^{-1} (C=O) and no hydroxyl band. This result suggests that the excess of chlorine caused the oxidation of hydroxyl at C-4′.

4-(3′-Oxocyclohexyl)phenylsuccinic acid (**12b**) was similarly synthesized in the procedures shown in Chart 2. **12b** and its ethylene acetal derivative (**11b**) could not be isolated as crystals, since each of them has two asymmetric carbons in its molecule and thus is composed of a pair of racemic diastereoisomers. The anhydride (**22**) of **12b**, although it was also a diastereoisomeric mixture, was obtained as colorless crystals, mp 111—113°, from the etherial solution. The intramolecular cyclization of **22** with aluminum chloride in dichloromethane gave quantitatively 3-oxo-5-(3′-oxocyclohexyl)indan-1-carboxylic acid (**23**), which was separated into each of racemic diastereoisomers, mp 160—164° and mp 188—192°, respectively, by fractionating recrystallization from benzene. For convenience, we call the former α-isomer (**23α**) and the latter β-isomer (**23β**). **23α** and **23β** thus obtained were converted to the corresponding α- and β-diastereoisomers of 5-(*cis*-3′-hydroxycyclohexyl)indan-1-carboxylic acid (**25α** and **25β**), respectively, in the procedures shown in Chart 4 which involved catalytic hydrogenation of the 3-oxo group and subsequent sodium borohydride reduction of the 3′-oxo group. In these hydride reductions, diastereoisomeric *trans*-3′-hydroxy compounds (**26α** and **26β**) were produced as minor products. The conformation of the hydroxyl groups at C-3′ in these four compounds (**25α**, **25β**, **26α** and **26β**) was confirmed by the NMR and IR spectra as described above in the case of 4′-hydroxy compounds (**16** and **17**). Chlorination of **25α** and **25β** gave α- and β-diastereoisomers of 6-chloro-5-(*cis*-3′-hydroxycyclohexyl)indan-1-carboxylic acid (**27α** and **27β**), respectively, and the reaction of **26α** and **26β** gave the corresponding diastereoisomeric 6-chloro derivatives (**28α** and **28β**), which have not been found in the metabolites of TAI-284 in rats.

Diastereoisomeric relationship between **27α** and **27β** was confirmed by epimerization on alkaline treatment of each isomer: when **27α** or **27β** was heated in an aqueous sodium hydroxide solution, both isomers gave the same 1:1 mixture of **27α** and **27β** as a result of epimerization at C-1, as shown in Chart 5. Under these conditions, (*R*)-(−)-TAI-284 gave (±)-TAI-284.

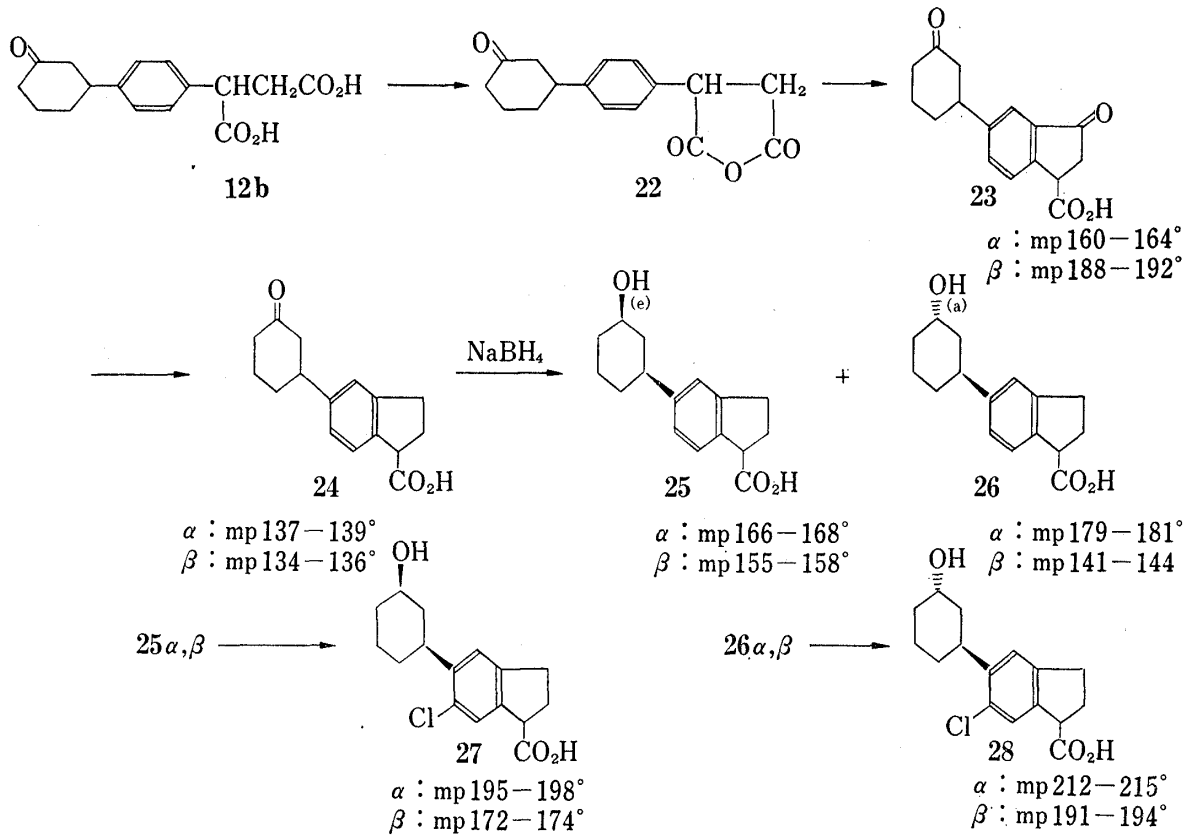
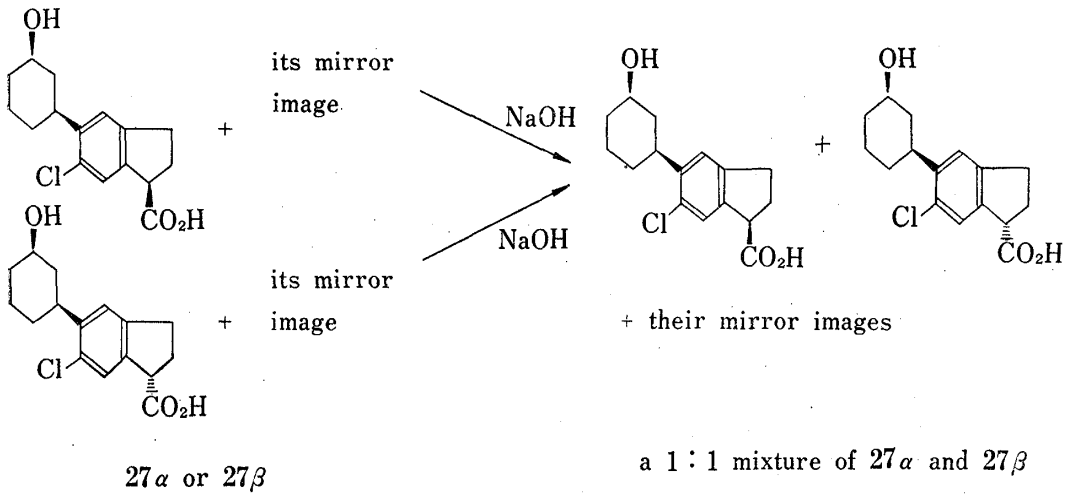


Chart 4



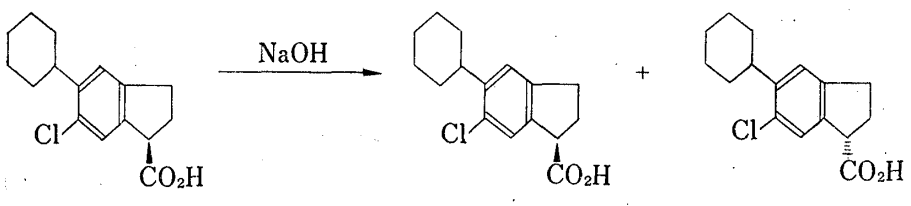


Chart 5

It was noted that diastereoisomeric α- and β-forms of 6-chloro compounds (**27** and **28**) showed different *Rf*-values in TLC while both diastereoisomeric forms of dechloro compounds (**23**—**26**) showed the same *Rf*-value. These results might be explained on the basis of a restricted rotation due to a steric hindrance by the chlorine substitutent at C-6. Fig. 2 shows conformational equilibria of **25** and **27**: among four stereoisomeric structures of each compound, only a pair of α- and β-isomers having *S*-configuration at C-1 is depicted. Although a free rotation about the single bond between the cyclohexane ring and indan moiety is permitted in the structure of **25**, the structure of **27** has some hindrance to rotation by a steric interaction between a chlorine atom at C-6 and axial hydrogens at C-2′ and 6′. Therefore it can be assumed that, of both diastereoisomeric structures of **27**, one has a structural feature in which the hydroxyl on the cyclohexane ring and the carboxyl group at C-1 exist in the same direction and the other in the opposite direction so as to give the great difference in dipole-moment of their molecules and hence in the behavior in TLC.

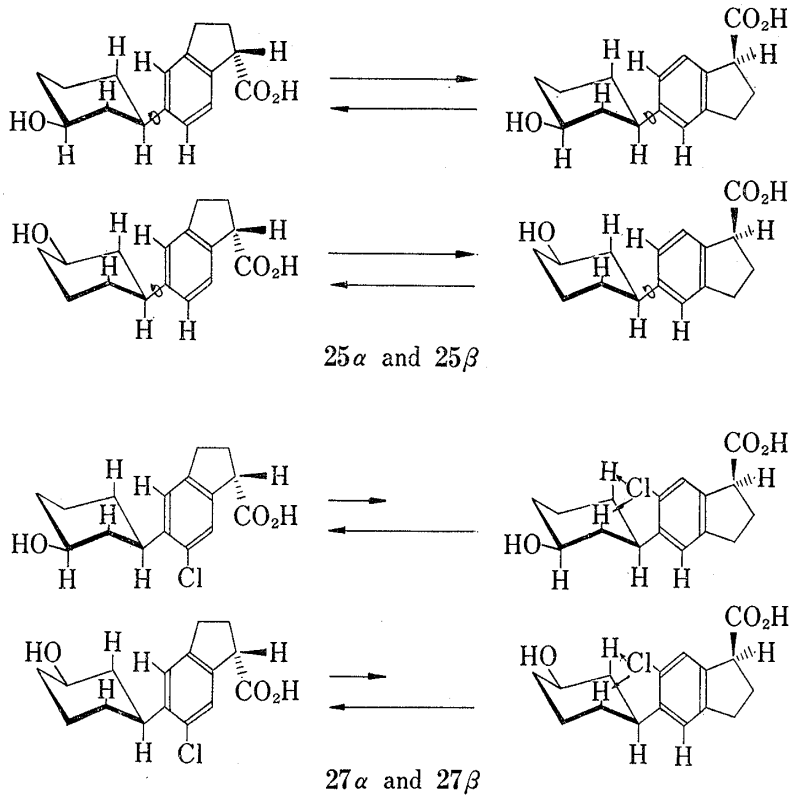


Fig. 2. . Conformational Equilibria of **25** and **27**

TABLE I. Chemical Shifts of the Methyl Groups of Methyl Esters of **25** and **27** induced by $Eu(fod)_3$[a]

Compound	Chemical shifts[b] (Hz) $Eu(fod)_3$ (mole equivalent)			
	0.1	0.2	0.3	0.4
Methyl ester of **25α**	—	25	—	50
Methyl ester of **25β**	—	25	—	50
Methyl ester of **27α**	10	22	36	57
Methyl ester of **27β**	12.5	27	44	69

a) solvents: $CDCl_3$
b) All four compounds show their methyl signals at 3.70 ppm in the absence of $Eu(fod)_3$.

This structural assumption was supported by NMR spectroscopy using a shift reagent. The spectrum of a 1: 2 mixture of methyl esters of **27α** and **27β** in deuterochloroform solution showed a single peak corresponding to their methyl groups, but when europium (III) tris 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione [Eu(fod)$_3$] was added to the solution, the single peak was separated into two peaks in the ratio 1: 2. On the other hand the spectra of a 1: 2 mixture of methyl esters of **25α** and **25β** showed only a single methyl peak even when 0.4 mole equivalent of Eu(fod)$_3$ was added to the solution (Table I). These results indicate that the distances between 1-carboxyl groups and 3'-hydroxyl ones are different in **27α** and **27β**, but almost equal in **25α** and **25β** owing to the conformational mobility.

Finally metabolites IIa, IIb, III and IV were directly compared with authentic compounds prepared in this study by TLC and NMR and IR spectra and confirmed to be identical with **21**, **27β**, **20** and **27α**, respectively. Biological effects of these compounds will be published elsewhere by Kuzuna, *et al.*,[13] biologists of our research division.

Experimental[14]

4-(*trans*-4'-Acetoxycyclohexyl)benzalmalononitrile (2)——To a stirred solution of 24 g of chloromethylenemalononitrile[15] in 600 ml of CH_2Cl_2 was added 44 g of *trans*-4-acetoxycyclohexylbenzene (1) and 80 g of pulverized anhydrous $AlCl_3$ at −25°. The stirred mixture was warmed gently until the reaction started and the temperature began to rise. After being stirred for 1 hr at 10—20°, the reaction mixture was poured into 2 liters of 12% HCl. The CH_2Cl_2 layer was separated. The aqueous layer was extracted with $CHCl_3$. The combined organic solution was washed with dilute HCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was treated with ether. The resulting solid was collected by filtration, dried and recrystallized from MeOH to give 16.2 g (33.3%) of **2** as colorless crystals, mp 142—144°. *Anal.* Calcd. for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.69; H, 6.07; N, 9.51. IR ν_{max}^{Nujol} cm^{-1}: 2220 (CN), 1715 (C=O). NMR (in $CDCl_3$) δ: 7.58 (4H, q, J=8.4 Hz, aromatic protons), 7.69 (1H, s, CH=C<), 4.74 (1H, m, $C_{4'}$–H), 2.60 (1H, m, $C_{1'}$–H), 2.04 (3H, s, CH_3).

α-[4-(*trans*-4'-Acetoxycyclohexyl)phenyl]-α,β,β-tricyanoethane (3)——To a stirred solution of 26.4 g of **2** in 260 ml of EtOH was added a solution of 5.2 g of NaCN in 30 ml of H_2O. After being stirred for 4 hr at room temperature, the reaction mixture was poured into 2.6 liters of H_2O, acidified with 12 ml of concentrated HCl and extracted with AcOEt. The extract was washed with an aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue was chromatographed on silica gel with benzene–AcOEt (10: 1) to give 13.5 g of **3** as brownish crystals. Recrystallization from 300 ml of EtOH gave 10.9 g (38%) of **3** as colorless crystals, mp 170—175° (decomp.). *Anal.* Calcd. for $C_{19}H_{19}O_2N_3$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.21; H, 6.00; N, 13.22. IR ν_{max}^{Nujol} cm^{-1}: 2250 (CN), 1715 (C=O). NMR (in d_6-DMSO) δ: 7.42 (4H, s, aromatic protons), 5.60 (2H, q, J=6 Hz, >CH–CH<), 4.66 (1H, m, $C_{4'}$–H), 2.56 (1H, m, $C_{1'}$–H), 1.99 (3H, s, CH_3).

4-(*trans*-4'-Hydroxycyclohexyl)phenylsuccinic Acid (4)——A suspension of 2.0 g of **3** in 40 ml of 20% HCl was heated under reflux for 3 hr. After being cooled, the reaction mixture was extracted with ether. The etherial solution was washed with H_2O and extracted with an aqueous solution of NaOH. The extract was washed with ether, treated with charcoal, acidified with dilute HCl and extracted with AcOEt. The extract was washed with an aqueous solution of NaCl and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel impregnated with 1% oxalic acid with $CHCl_3$–AcOEt (1: 1) to give **4**, which was recrystallized from AcOEt to give 110 mg (6%) of colorless crystals, mp 215—218°. *Anal.* Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.73; H, 7.23. IR ν_{max}^{Nujol} cm^{-1}: 3390 (OH), 1700 (C=O), 1065 (C–OH).

4-(*trans*-4'-Acetoxycyclohexyl)phenylsuccinic Anhydride (5)——A solution of 80 mg of **4** in 4 ml of Ac_2O was heated under reflux for 3 hr, and then concentrated under reduced pressure. To the oily residue was added hexane and ether. The resulting precipitates were collected by filtration and recrystallized from benzene–ether to give 67 mg (78%) of **5** as colorless crystals, mp 164—167°. The conformation of the acetoxyl group at C-4' in **5** was confirmed on the basis of its NMR spectrum.[11] *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.34; H, 6.44. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1780 (CO–O–CO), 1720 (OCOCH$_3$). NMR (in $CDCl_3$) δ: 7.20 (4H, s, aromatic protons), 4.80 (1H, m, $C_{4'}$–H), 4.36 (1H, q, –CH–), 2.8—4.0 (2H,

13) S. Kuzuna, N. Matsumoto and K. Kawai, unpublished.
14) Melting points are uncorrected. IR spectra were obtained with a Hitachi-215 spectrophotometer and NMR spectra with a Varian A-60 spectrometer using TMS as internal standard.
15) K. Friedrich and W. Ertel, *Synthesis*, 2, 23 (1970).

m, $-CH_2-$), 2.05 (3H, s, CH_3).

4-(4′- and 3′-Oxocyclohexyl)benzylchloride (8a and 8b)——To a stirred, ice-cooled solution of 237.5 g of $TiCl_4$ in 1250 ml of CH_2Cl_2 was added a solution of 87.2 g of 4-phenylcyclohexanone (**7a**) in 375 ml of CH_2Cl_2 and a solution of 60.4 g of chloromethyl methyl ether in 200 ml of CH_2Cl_2 dropwise. Stirring and cooling were continued for 1 hr. A solution of 60.4 g of chloromethyl methyl ether in 200 ml of CH_2Cl_2 was further added dropwise to the reaction mixture. After being stirred for additional 1.5 hr, the reaction mixture was poured into 2.75 liters of 12% HCl. The CH_2Cl_2 layer was separated, washed with an aqueous solution of $NaHCO_3$ and H_2O successively, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The oily residue was chromatographed on silica gel with $CHCl_3$, and the eluate was further purified by distillation to give **8a** as a colorless oil, bp 150—170° (0.7 mmHg), which crystallized on standing at room temperature. Recrystallization from hexane gave 41.6 g (38%) of **8a** as colorless crystals, mp 76—79°. *Anal.* Calcd. for $C_{13}H_{15}OCl$: C, 70.10; H, 6.79; Cl, 15.92. Found: C, 70.09; H, 6.58; Cl, 15.92. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in CCl_4) δ: 7.24 (4H, s, aromatic protons), 4.52 (2H, s, CH_2Cl), 3.0 (1H, m, $C_{1'}$–H). **8b** was obtained from 3-phenylcyclohexanone (**7b**) using the similar procedure as a colorless oil, bp 141—159° (0.3 mmHg) (40% yield). *Anal.* Calcd. for $C_{13}H_{15}OCl$: C, 70.09; H, 6.79; Cl, 15.92. Found: C, 70.53; H, 6.70; Cl, 16.00. IR ν_{max}^{Neat} cm^{-1}: 1700 (C=O). NMR (in CCl_4) δ: 7.22 (4H, q, J=7.5 Hz, aromatic protons), 4.50 (2H, s, CH_2Cl), 2.9 (1H, m, $C_{1'}$–H).

4-(4′- and 3′-Ethylenedioxycyclohexyl)benzylchloride (9a and 9b)——A mixture of 23.1 g of **8a**, 0.3 g of *p*-toluenesulfonic acid monohydrate and 8.4 g of ethylene glycol in 200 ml of toluene was heated under reflux for 6 hr. After being cooled, benzene was added to the reaction solution, and the mixture was washed with an aqueous solution of $NaHCO_3$ and H_2O successively and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave **9a** quantitatively as colorless crystals, which was used for the subsequent reaction without further purification. The analytical sample, mp 50—52°, was obtained by recrystallization from hexane. *Anal.* Calcd. for $C_{15}H_{19}O_2Cl$: C, 67.54; H, 7.18; Cl, 13.29. Found: C, 67.61; H, 7.19; Cl, 13.03. NMR (in $CDCl_3$) δ: 7.26 (4H, s, aromatic protons), 4.54 (2H, s, CH_2Cl), 3.97 (4H, s, OCH_2CH_2O). **9b** was obtained from **8b**, using the similar procedure, as a colorless oil, bp 138—143° (0.08 mmHg) (91% yield). *Anal.* Calcd. for $C_{15}H_{19}O_2Cl$: C, 67.17; H, 7.18; Cl, 13.29. Found: C, 67.79; H, 7.30; Cl, 13.59. NMR (in CCl_4) δ: 7.15 (4H, q, J=8 Hz, aromatic protons), 4.46 (2H, s, CH_2Cl), 3.86 (4H, s, OCH_2CH_2O).

4-(4′- and 3′-Ethylenedioxycyclohexyl)phenylacetonitrile (10a and 10b)——A mixture of 27.6 g of **9a** and 7.4 g of NaCN in 300 ml of 70% EtOH was heated under reflux for 3.5 hr, and concentrated under reduced pressure. To the residue was added 300 ml of H_2O, and the mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was treated with hexane. The resulting solid was collected by filtration, dried and recrystallized from cyclohexane to give 20.6 g (77.5%) of **10a** as colorless crystals, mp 83—85°. *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.57; H, 7.43; N, 5.17. IR ν_{max}^{Nujol} cm^{-1}: 2240 (CN). NMR (in $CDCl_3$) δ: 7.23 (4H, s, aromatic protons), 3.96 (4H, s, OCH_2CH_2O), 3.67 (2H, s, CH_2CN). **10b** was obtained from **9b**, using the similar procedure, as colorless crystals, mp 71—78° (60% yield). *Anal.* Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.81; H, 7.61; N, 5.70. IR ν_{max}^{Nujol} cm^{-1}: 2250 (CN). NMR (in $CDCl_3$) δ: 7.25 (4H, s, aromatic protons), 3.99 (4H, s, OCH_2CH_2O), 3.69 (2H, s, CH_2CN).

4-(4′-Ethylenedioxycyclohexyl)phenylsuccinic Acid (11a)——To a stirred suspension of 14.2 g of NaOEt (prepared from 4.8 g of metallic Na) in 60 ml of dry toluene was added dropwise a solution of 51.7 g of **10a** in 240 ml of dry toluene and 105 ml of diethyl carbonate. The mixture was heated on an oil bath with stirring, and the resulting EtOH was distilled off as it was formed. During this reaction, the volume of the reaction mixture was maintained constant by means of adding dry toluene dropwise. After the temperature of the vapor had risen to 110—112°, the heating was stopped. To the cooled reaction mixture was added 35 g of ethyl bromoacetate, and the mixture was heated under reflux with vigorous stirring for 1 hr. After being cooled, the reaction mixture was poured into an aqueous solution of NaCl and extracted with ether. The extract was washed with an aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. To the residual oil was added 800 ml of ethylene glycol and 92 g of KOH, and the mixture was heated under reflux for 4 hr under nitrogen atmosphere. After being cooled, the reaction mixture was poured into 2.4 liters of H_2O, washed with ether, acidified with dilute HCl and extracted with AcOEt. The extract was washed with an aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was treated with 150 ml of hexane and 150 ml of ether. The resulting solid was collected to give 41.1 g (61%) of **11a**, which was used for the subsequent reaction without further purification. The analytical sample was obtained by recrystallization from AcOEt as colorless crystals, mp 182—183.5°. *Anal.* Calcd. for $C_{18}H_{22}O_6$: C, 64.65; H, 6.63. Found: C, 64.93; H, 6.84. IR ν_{max}^{Nujol} cm^{-1}: 1725, 1685 (C=O). NMR (in d_6-DMSO) δ: 7.14 (4H, s, aromatic protons), 3.84 (4H, s, OCH_2-CH_2O), 3.83 (1H, q, –CH–), 2.70 (2H, m, $-CH_2-$).

4-(4′-Oxocyclohexyl)phenylsuccinic Acid (12a)——A solution of 17.5 g of **11a** in 350 ml of 50% EtOH and 17.5 ml of AcOH was heated under reflux for 4 hr, and then concentrated under reduced pressure. The residue was dissolved in AcOEt and the solution was washed with H_2O, treated with charcoal, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was treated with 100 ml of ether. The resulting solid was collected to give 13.7 g (90%) of **12a**, which was used for the subsequent

reaction without further purification. The analytical sample was obtained by recrystallization from AcOEt as colorless crystals, mp 140—143°. *Anal.* Calcd. for $C_{16}H_{18}O_5 \cdot H_2O$: C, 62.32; H, 6.54. Found: C, 62.22; H, 6.43. IR ν_{max}^{Nujol} cm^{-1}: 1690 (C=O). NMR (in d_6-DMSO) δ: 7.19 (4H, s, aromatic protons), 3.84 (1H, q, –CH–), 2.70 (2H, m, $-CH_2-$).

4-(4′-Oxocyclohexyl)phenylsuccinic Anhydride (13)——A solution of 12.7 g of **12a** in 70 ml of Ac_2O was heated under reflux for 1 hr, and then concentrated under reduced pressure. The residue was treated with 80 ml of ether and 5 ml of benzene. The resulting solid was collected to give 8.8 g (74%) of **13**, which was recrystallized from benzene–ether to give colorless crystals, mp 112—113.5°. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.42; H, 5.93. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1780 (CO–O–CO), 1705 (C=O). NMR (in $CDCl_3$) δ: 7.24 (4H, s, aromatic protons), 4.34 (1H, q, –CH–), 3.26 (2H, m, $-CH_2-$).

3-Oxo-5-(4′-oxocyclohexyl)indan-1-carboxylic Acid (14)——A solution of 8.8 g of **13** in 80 ml of CH_2Cl_2 was added dropwise to a stirred, ice-cooled suspension of 43.1 g of pulverized anhydrous $AlCl_3$ in 150 ml of CH_2Cl_2. The mixture was stirred under ice-cooling for 3 hr and then at room temperature for 1 hr. To the stirred, cooled reaction mixture was added dropwise cooled dilute HCl. The organic layer was separated, washed with an aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was treated with 100 ml of hexane and 70 ml of AcOEt. The resulting solid was collected to give 7.8 g (89%) of **14**, which was recrystallized from AcOEt–hexane to give colorless crystals, mp 170—173°. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.57; H, 5.94. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1680 (C=O). NMR (in $CDCl_3$) δ: 7.64 (1H, d, J=2 Hz, C_4–H), 7.53 (1H, q, C_6–H), 7.71 (1H, d, J=9 Hz, C_7–H), 4.29 (1H, q, C_1–H), 3.17 (1H, q, C_2–H), 2.88 (1H, q, C_2–H).

5-(4′-Oxocyclohexyl)indan-1-carboxylic Acid (15)——4 g of **14** was hydrogenated over 2.4 g of 5% Pd–C in 400 ml of AcOH at room temperature. After 5 hr the catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was dissolved in AcOEt and the solution was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was treated with 40 ml of hexane. The resulting solid was collected to give 3.3 g (87%) of **15**, which was recrystallized from AcOEt to give colorless crystals, mp 124—127°. The analytical sample was obtained by recrystallization from CCl_4, mp 126—128°. *Anal.* Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.15 H, 6.73. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). NMR (in $CDCl_3$) δ: 7.34 (1H, d, C_7–H), 7.08 (1H, s, C_4–H), 7.03 (1H, d, C_6–H), 4.01 (1H, t, J=7 Hz, C_1–H).

5-(*trans*-4′-Hydroxycyclohexyl)indan-1-carboxylic Acid (16) and Its Methyl Ester (18)——To a stirred solution of 296 mg of $NaBH_4$ in 10 ml of 0.05N aqueous solution of NaOH was added dropwise a solution of 4 g of **15** in 30 ml of 1N aqueous solution of NaOH, and the mixture was stirred for 4 hr at room temperature. To the cooled reaction mixture was added dilute HCl and $CHCl_3$. The organic layer was separated, washed with dilute HCl and H_2O successively, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was treated with ether. The resulting solid was collected to give 3.2 g (80%) of **16**, which was recrystallized from AcOEt to give colorless crystals, mp 177—179°. *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.54; H, 7.69. IR ν_{max}^{Nujol} cm^{-1}: 3375 (OH), 1700 (C=O), 1060 (C–OH). Treatment of **16** with CH_2N_2 gave its methyl ester (**18**). Colorless crystals of **18** was obtained by recrystallization from hexane, mp 109—110°. *Anal.* Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.47; H, 8.30. IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 1730 (C=O), 1070 (C–OH). NMR (in $CDCl_3$) δ: 7.22, 6.96 (2H, q, J=9 Hz, C_6– and C_7–H), 7.02 (1H, s, C_4–H), 3.96 (1H, t, C_1–H), 3.68 (3H, s, CH_3), 3.67 (1H, m, $C_{4'}$–H).

5-(*cis*-4′-Hydroxycyclohexyl)indan-1-carboxylic Acid (17) and Its Methyl Ester (19)——A mixture of 5 g of **15**, 450 mg of PtO_2, 200 ml of AcOH and 20 ml of concentrated HCl was shaken under a hydrogen atmosphere, till 720 ml of hydrogen was absorbed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. To the residue was added a solution of 5 g of NaOH in 200 ml of 50% EtOH and the mixture was heated under reflux for 4 hr. The reaction solution was concentrated under reduced pressure, and the residue was acidified with dilute HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residual solid was recrystallized from acetone to give 3.2 g (64%) of **17**. Further recrystallization from AcOEt gave colorless crystals, mp 186—188°. *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.59; H, 7.61. IR ν_{max}^{Nujol} cm^{-1}: 3340 (OH), 1690 (C=O), 950 (C–OH). Treatment of **17** with CH_2N_2 gave its methyl ester (**19**). Colorless crystals of **19** was obtained by recrystallization from hexane, mp 63—65°. *Anal.* Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.40; H, 8.30. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 1730 (C=O), 950 (C–OH). NMR (in $CDCl_3$) δ: 7.27, 7.03 (2H, q, J=9 Hz, C_6– and C_7–H), 7.10 (1H, s, C_4–H), 4.10 (1H, s, $C_{4'}$–H), 4.0 (1H, t, C_1–H), 3.67 (3H, s, CH_3).

6-Chloro-5-(*trans*-4′-hydroxycyclohexyl)indan-1-carboxylic Acid (20)——A solution of 975 mg of Cl_2 in 15 ml of CH_3CN was added dropwise to a stirred, ice-cooled solution of 3.08 g of **16** in 225 ml of CH_3CN. The mixture was stirred for 3 hr under cooling. A solution of 390 mg of Cl_2 in 6 ml of CH_3CN was further added to the mixture, and the stirring was continued for 3 hr. The reaction mixture was concentrated under reduced pressure. To the residue was added a solution of CH_2N_2 in ether and the resulting solution was concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–acetone (60: 1) to give 800 mg of the methyl ester of **20** as colorless crystals, mp 80—84°. A mixture of 800 mg of this ester and 2 g of NaOH in 80 ml of 50% EtOH was heated under reflux for 5 hr. After being cooled, the

reaction solution was concentrated under reduced pressure. The residual aqueous solution was washed with ether, acidified with dilute HCl and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residual solid was recrystallized from benzene to give 460 mg (13.4%) of **20** as colorless crystals, mp 188—190°. *Anal.* Calcd. for $C_{16}H_{19}O_3Cl$: C, 65.19; H, 6.50; Cl, 12.03. Found: C, 64.91; H, 6.61; Cl, 11.89. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1705 (C=O), 1070 (C–OH). NMR (in $CDCl_3$+d_6-DMSO) δ: 7.35 (1H, s, C_7–H), 7.09 (1H, s, C_4–H), 3.91 (1H, t, C_1–H), 3.55 (1H, m, $C_{4'}$–H). Methyl ester of **20**: *Anal.* Calcd. for $C_{17}H_{21}O_3Cl$: C, 66.13; H, 6.86; Cl, 11.48. Found: C, 65.71; H, 6.77; Cl, 11.71. IR ν_{max}^{Nujol} cm^{-1}: 3375 (OH), 1740 (C=O). NMR (in $CDCl_3$) δ: 7.31 (1H, s, C_7–H), 7.06 (1H, s, C_4–H), 3.96 (1H, t, C_1–H), 3.70 (3H, s, CH_3).

6-Chloro-5-(*cis*-4′-hydroxycyclohexyl)indan-1-carboxylic Acid (21)——According to the procedure similar to the one described in the case of **20**, **21** was prepared from **17** and recrystallized from acetone to give colorless crystals, mp 206—208° (23% yield). *Anal.* Calcd. for $C_{16}H_{19}O_3Cl$: C, 65.19; H, 6.50; Cl, 12.03. Found: C, 65.28; H, 6.44; Cl, 12.07. IR ν_{max}^{KBr} cm^{-1}: 3325 (OH), 1705 (C=O), 960 (C–OH). NMR (in d_6-DMSO) δ: 7.26 (1H, s, C_7–H), 7.19 (1H, s, C_4–H), 3.9 (2H, m, C_1– and $C_{4'}$–H).

4-(3′-Oxocyclohexyl)phenylsuccinic Anhydride (22)——According to the procedures similar to the ones described in the case of 4′-oxo compound (**13**), **22** was prepared from **10b** in three steps. Intermediary succinic acids (**11b** and **12b**) could not be isolated as crystals and thus oily crude products were used for the subsequent reactions without further purification, but **22** was precipitated as colorless crystals, mp 111—113°, from ether (27.9%). The analytical sample was obtained by recrystallization from ether, mp 114—116°. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.55; H, 6.06. IR ν_{max}^{Nujol} cm^{-1}: 1860, 1790 (CO–O–CO), 1700 (C=O). NMR (in $CDCl_3$) δ: 7.21 (4H, s, aromatic protons), 4.31 (1H, q, –CH–), 3.25 (2H, m, $-CH_2-$).

3-Oxo-5-(3′-oxocyclohexyl)indan-1-carboxylic Acids (23α and 23β)——A solution of 8.2 g of **22** in 80 ml of CH_2Cl_2 was added dropwise to a stirred, ice-cooled suspension of 40 g of pulverized anhydrous $AlCl_3$ in 160 ml of CH_2Cl_2. The mixture was stirred under cooling for 1.5 hr and then at room temperature for 1 hr. To the stirred, cooled reaction mixture was added dropwise cooled dilute HCl. The organic layer was separated, washed with H_2O and extracted with a solution of 15 g of $NaHCO_3$ in 200 ml of H_2O. The extract was washed with ether and acidified with dilute HCl. The resulting precipitates were extracted with AcOEt and the organic solution was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residual solid was recrystallized from a small amount of AcOEt to give 2.6 g of **23α** as colorless crystals. The analytical sample was obtained by repeated recrystallization from AcOEt, mp 161—164°. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.82; H, 5.84. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1710, 1700 (C=O). NMR (in d_6-DMSO) δ: 7.63 (2H, s, C_6– and C_7–H), 7.54 (1H, s, C_4–H), 4.24 (1H, t, C_1–H), 3.06 (1H, m, $C_{1'}$–H), 2.86 (2H, d, C_2–H). The mother liquor of the first isolation of the crystals of **23α** was concentrated to dryness under reduced pressure. The residual solid was treated with AcOEt. The undissolved solid was collected by filtration and recrystallized from acetone to give colorless crystals of **23β**, mp 188—192°. *Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.79; H, 5.87. IR ν_{max}^{Nujol} cm^{-1}: 1760, 1720, 1700 (C=O). The NMR spectrum of **23β** was identical with that of **23α**.

5-(3′-Oxocyclohexyl)indan-1-carboxylic Acids (24α and 24β)——According to the procedure similar to the one described in the case of **15**, **24α** and **24β** were prepared from **23α** and **23β**, respectively. **24α** was obtained by recrystallization from benzene-cyclohexane as colorless crystals, mp 137—139° (89% yield). *Anal.* Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 73.91; H, 7.02. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1710 (C=O). NMR (in $CDCl_3$) δ: 7.04 (1H, s, C_4–H), 7.15 (2H, q, C_6– and C_7–H), 3.99 (1H, t, C_1–H). **24β** was obtained by recrystallization from ether–petroleum ether as colorless crystals, mp 134—136°. (90% yield). *Anal.* Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.64; H, 7.13. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1700 (C=O). The NMR spectrum of **24β** was identical with that of **24α**.

5-(*cis*-3′-Hydroxycyclohexyl)indan-1-carboxylic Acids (25α and 25β) and Their *trans*-Isomers (26α and 26β)——To a stirred, ice-cooled solution of 450 mg of $NaBH_4$ in 18 ml of 0.05N aqueous solution of NaOH was added dropwise a solution of 5.9 g of **24α** in 45 ml of 1N aqueous solution of NaOH, and the mixture was stirred under cooling for 1 hr and then at room temperature for 2.5 hr. To the cooled reaction mixture was added dilute HCl and $CHCl_3$. The organic layer was separated, washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The residual solid was recrystallized from AcOEt to give 4.4 g (75%) of **25α** as colorless crystals, mp 166—168°. *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.84; H, 7.44. IR ν_{max}^{Nujol} cm^{-1}: 3375 (OH), 1710 (C=O), 1045 (C–OH). NMR (in D_2O+NaOD) δ: 7.42 (1H, d, C_7–H), 7.32 (1H, s, C_4–H), 7.26 (1H, d, C_6–H), 4.04 (1H, t, C_1–H). The mother liquor of the first isolation of the crystals of **25α** was concentrated under reduced pressure. The residue was chromatographed on silica gel impregnated with 1% oxalic acid to give 550 mg of **26α**, which was recrystallized from AcOEt to give 460 mg as colorless crystals, mp 179—181°. *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.82; H, 7.80. IR ν_{max}^{Nujol} cm^{-1}: 3430 (OH), 1700 (C=O), 970 (C–OH). NMR (in $CDCl_3$+d_6-DMSO) δ: 7.23 (1H, d, C_7–H), 7.03 (1H, s, C_4–H), 6.98 (1H, d, C_6–H), 4.09 (1H, s, $C_{3'}$–H), 3.90 (1H, t, C_1–H). **25β** and **26β** were prepared from **24β** using the similar procedure as described above. **25β**: mp 155—158° (AcOEt). *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.52; H, 7.62.

IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1705 (C=O), 1050 (C–OH). The NMR spectrum of **25β** was identical with that of **25α**. **26β**: mp 141—144° (AcOEt). *Anal.* Calcd. for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.78; H, 7.77. IR ν_{max}^{Nujol} cm^{-1}: 3330 (OH), 1725, 1695 (C=O), 975 (C–OH). The NMR spectrum of **26β** was identical with that of **26α**.

6-Chloro-5-(*cis*-3′-hydroxycyclohexyl)indan-1-carboxylic Acids (27α and 27β) and Their *trans*-Isomers (28α and 28β)——A solution of 1.6 g of Cl_2 in 30 ml of CH_3CN was added dropwise to a stirred, ice-cooled solution of 3.0 g of **25α** in 300 ml of CH_3CN. The mixture was stirred under cooling for 1 hr and at 25° for 1.5 hr, and then concentrated under reduced pressure. The residue was dissolved in AcOEt and the solution was washed with H_2O, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel impregnated with 1% oxalic acid with benzene–AcOEt (4: 1) to give 1.4 g of **27α**, which was recrystallized from AcOEt to give 1.15 g (34%) as colorless crystals, mp 195—198°. *Anal.* Calcd. for $C_{16}H_{19}O_3Cl$: C, 65.19; H, 6.50; Cl, 12.03. Found: C, 65.16; H, 6.34; Cl, 12.20. IR ν_{max}^{Nujol} cm^{-1}: 3375 (OH), 1700 (C=O), 1050 (C–OH). NMR (in $CDCl_3$+d_6-DMSO) δ: 7.35 (1H, s, C_7–H), 7.10 (1H, s, C_4–H), 3.91 (1H, t, C_1–H), 3.65 (1H, br.s, C_3'–H). **27β**, **28α** and **28β** were prepared from **25β**, **26α** and **26β**, respectively, using the similar procedure as described above. **27β**: mp 172—174° (AcOEt). *Anal.* Calcd. for $C_{16}H_{19}O_3Cl$: C, 65.19; H, 6.50; Cl, 12.03. Found: C, 65.45; H, 6.50; Cl, 11.78. IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH), 1710 (C=O), 1060 (C–OH). The NMR spectrum of **27β** was identical with that of **27α**. **28α**: mp 212—215° (AcOEt). *Anal.* Calcd. for $C_{16}H_{19}O_3Cl$: C, 65.19; H, 6.50; Cl, 12.03. Found: C, 65.28; H, 6.54; Cl, 11.89. IR ν_{max}^{Nujol} cm^{-1}: 3420 (OH), 1705 (C=O), 970 (C–OH). NMR (in $CDCl_3$+d_6-DMSO) δ: 7.36 (1H, s, C_7–H), 7.14 (1H, s, C_4–H), 4.15 (1H, s, $C_{3'}$–H), 3.95 (1H, t, C_1–H). **28β**: mp 191—194°. The structure of this compound was confirmed on the basis of its NMR spectrum, which was identical with that of **28α**.

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