Antiinflammatory and Analgesic Diastereoisomeric Derivatives of Indan-5-acetic Acid

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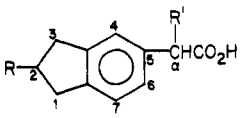
Various 2-alkyl-α-methyl- and 2-alkylindan-5-acetic acids have been prepared. The acids, which can exist in two diastereoisomeric forms that cannot be separated by crystallization or chromatography, can be analyzed in their mixture by NMR in the presence of $Eu(dpm)_3$. It has been possible to reconstitute the two *pure racemic* 2-isopropyl-α-methylindan-5-acetic acids from their enantiomers obtained after resolution of the mixtures through salts with various active bases. The relative configuration of the two asymmetric centers of one of the diastereoisomers has been determined by X-ray crystallography. The absolute configurations of the resolved acids have been established by a comparative study of their CD curves. The antiinflammatory and analgesic properties of these compounds as functions of their structure and stereochemistry are discussed.

Among the nonsteroid products showing antiinflammatory properties, the class of substituted arylacetic acids has undoubtedly been studied most widely; these acids have been the subject of several general reviews.[1-3]

The new derivatives of indan-5-acetic acid of the general formula 1 are among the highly active representatives of



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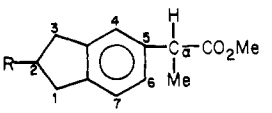
this series. These acids are obtained by three routes, which are summarized in Scheme I. The synthetic schemes involve, at a more or less advanced stage, the creation of a second center of asymmetry remote from the one already present. Consequently no asymmetric induction takes place and the final acids **7** contain roughly equal amounts of diastereoisomers. These mixtures have a sharp melting point that does not vary even after several crystallizations; the same applies to their salts (sodium, dicyclohexylamine, etc.). Chromatography of the methyl esters on a wide variety of columns was unsuccessful in separating the diastereoisomers. Other attempts at separation by high-pressure liquid chromatography or by zone melting likewise were unsuccessful.

It has been possible to solve this particularly difficult separation problem in the case of the compound which is most interesting from the pharmacological point of view, that of 2-isopropyl-α-methylindan-5-acetic acid (**7c**), by a method that could undoubtedly prove useful in other cases. It was thought that if the two *racemic* diastereoisomeric forms give solid solutions in all proportions, the *resolved* diastereoisomers might have a different behavior. In fact, recrystallization of the salts formed from mixtures of acids **7c** and certain chiral amines permits *simultaneous resolution* of the two diastereoisomers, which is accompanied by partial separation of the two optically active diastereoisomers. This mixture then becomes separable by crystallization.

The separation process based on this principle is summarized in Scheme II; its progress can be followed by NMR. The NMR spectra of mixtures of the diastereoisomeric methyl esters **8** derived from the acids **7** look like those of pure substances with the chemical shifts indicated in Table I. However, the addition of $Eu(dpm)_3$[4] to the solution leads to a splitting of the peaks of the MeO, H-4,

Table I. ^1H NMR Data for the Methyl Esters 8 of Acids 7[a]



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compd	proton	δ	$\Delta\delta/\Delta\delta^{OMe}$ [b]
8a-d	H-1,3	2.9, 2.5	
	H-2	2.3	
	H-4	6.97	0.68
	H-6	6.90	0.64
	H-7	6.99	0.14
	H α	3.52	1.13
	Me α	1.41	0.84
	Me ester	3.57	1
8a	Me (R)	1.14	
8b	Me (R)	0.97	
8c	Me (R)	0.97	
	H (R)	1.634	
8d	cyclohexyl (R)	1.2, 1.7	

[a] The spectra were recorded on a Varian HA-100 spectrometer, at 100 MHz and 30 ± 1 °C, in CCl_4. Chemical shifts (δ) are reported in parts per million relative to Me_4Si (δ = 0) as an internal reference. [b] In the presence of $Eu(dpm)_3$; Δδ = induced shift of a given signal; $\Delta\delta^{OMe}$ = induced shift of the OMe signal.

α-Me, and α-H signals and, in certain cases, of that of the radical R. This is sufficient to permit an estimation of the diastereoisomer composition.

In a pair of diastereoisomers, it is convenient to call A the isomer whose OMe signal undergoes the greatest induced shift. For mixtures in which the two constituents are no longer in equal proportions, it can be stated that all the signals of A are shifted further downfield than those of isomer B. The effect of $Eu(dpm)_3$ gives no clear indication of the relative stereochemistry of the diastereoisomers examined (see supplementary material).

In mixtures of *levorotatory* acids A and B obtained via the cinchonidine salt, and also in the *dextrorotatory* mixtures obtained by means of L-acetonamine,[5] the two diastereoisomers remain present in substantially equal amounts and are solid solutions.

On the other hand, resolution by means of the α-phenylethylamine salts is accompanied by partial separation of the diastereoisomers: the mixture is enriched with isomer A. A slow crystallization of this mixture (containing about 30% of B and 70% of A with the same

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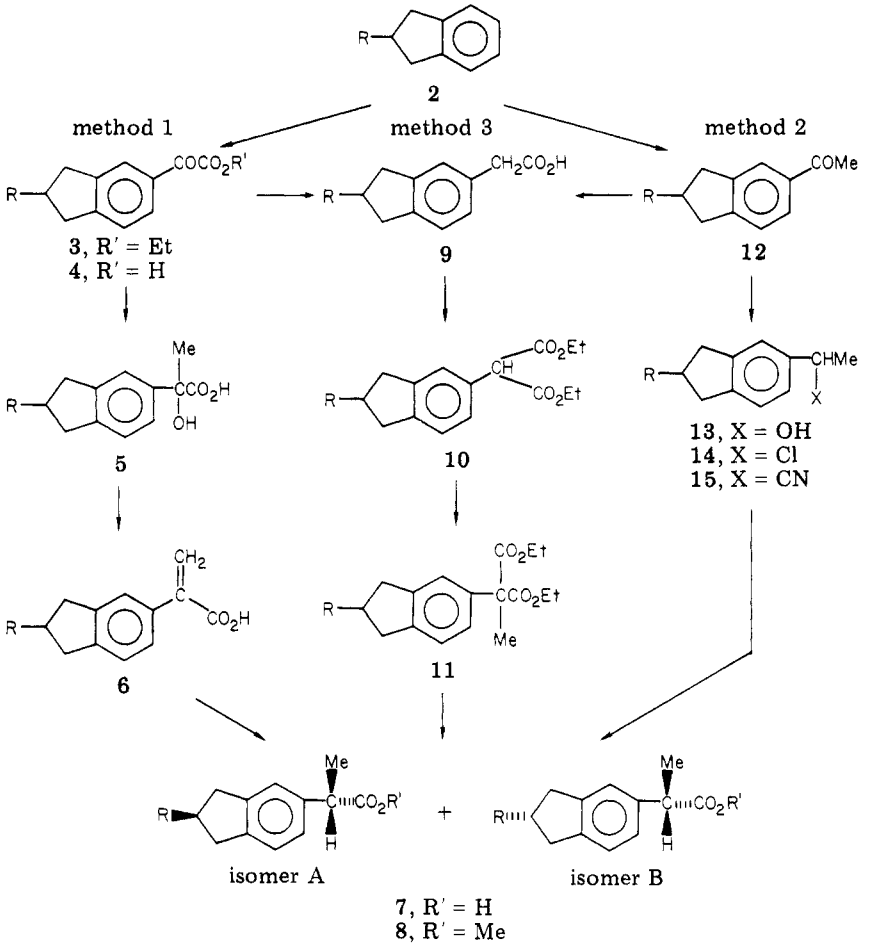
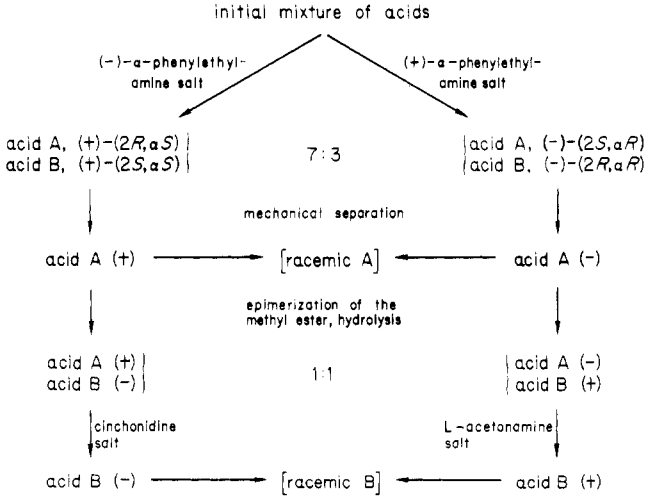
Scheme I



a, R = Me; b, R = Et; c, R = *i*-Pr; d, R = cyclohexyl

Scheme II. Separation of Diastereoisomeric 2-Isopropyl-α-methylindan-5-acetic Acids 7c



signs) provides two types of crystals sufficiently developed for separation by manual sorting. One of these forms consists of the pure A isomer. This separation may be performed with (+)- or (−)-α-phenylethylamine.

Access to the pure A isomers enabled us to obtain the B isomers. Thus, epimerization of the methyl ester obtained from A (+) in the presence of sodium methoxide leads after hydrolysis to a mixture containing equal proportions of the acids A (+) and B (−), which now differ only by the configuration of the carbon α to the acid function. At this stage, cinchonidine, which forms a sparingly soluble salt with the acid B (−) (see Scheme II), enables the mixture of epimeric acids to be separated. When the operation is performed in the antipodal series it gives access to the B (+) acid.

With these pure isomers available, the calorimetric recording of their melting enables temperatures and enthalpies to be measured with the aid of which it has been possible to calculate the phase diagrams of the binary mixtures of enantiomers.[6] These diagrams, with the experimental points that confirm them, are given in Figures 1–5 (see paragraph at end of paper regarding supplementary material). In particular, they provide clear evidence of the presumed existence of solid solutions between racemic diastereoisomers.

Relative and Absolute Configuration of 7c. A radiocrystallographic structure determination provides the only possible solution to this problem: this was performed on a sample of the diastereoisomer A (mp 65 °C; $[\alpha]^{25}_{578}$ +56°[7]). Figure 6 shows a combination of the two molecules. The diastereoisomer A has an *RS* or *SR* structure.

The absolute configuration of the acids A and B is easily deduced from the characteristics of their circular dichroism. The diastereoisomers A and B with opposite signs at 578 nm have opposite configurations at the carbon atoms in the position α to the acid function; this follows from the epimerization experiments prescribed above. The CD curves of the two diastereoisomers A and B of the same sign show a strong absorption band at 228 nm which, in acids of this type, is generally attributed to the $n \rightarrow \pi$ transition of the carboxylic chromophore. As Djerassi et al.[8] have shown, the sign of the Cotton effect of this band may be connected with the absolute configuration of a very

Table II. Pharmacological Properties of Substituted Indanacetic Acids 7 and 9

compd	isomer composition, A/B	ED_{50}, mg/kg po: carrageenan edema test	ED_{50}, mg/kg po: phenylquinone test	UD_{50}, mg/kg po, ulcerogenic act.
(±)-9a			175 (106.5-273.3)	
(±)-9b		>256	104 (68.0-152.7)	125
(±)-9c		155 (106.0-237.2)	57 (40.0-80.9)	335
(±)-7a	1/1		24 (15.3-37.3)	
(±)-7b	1/1	36 (15.1-94.2)	6 (3.9-10.2)	65
(±)-7c	1/1	29 (15.5-50.90)	9 (5.2-15.0)	62
(+)-7c	6/4	24 (4.7-139.2)	10 (6.2-15.9)	46
(−)-7c	1/1	32 (12.2-99.1)	17 (9.8-30.2)	87
(+)-7c	1/0		9 (5.1-17.1)	
ibuprofen		44 (18.7-103.1)	17 (11.7-26.4)	40

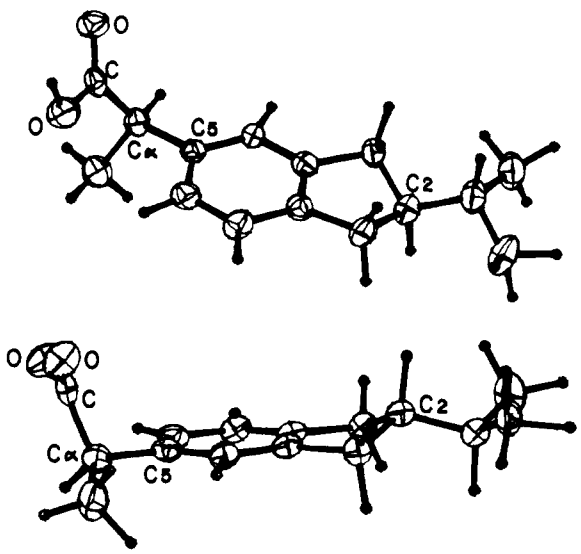


Figure 6. ORTEP drawing of acid **7c**, isomer A; the two independent molecules of configuration 2*S*,α*R* corresponding to the enantiomer (−)-A are represented.

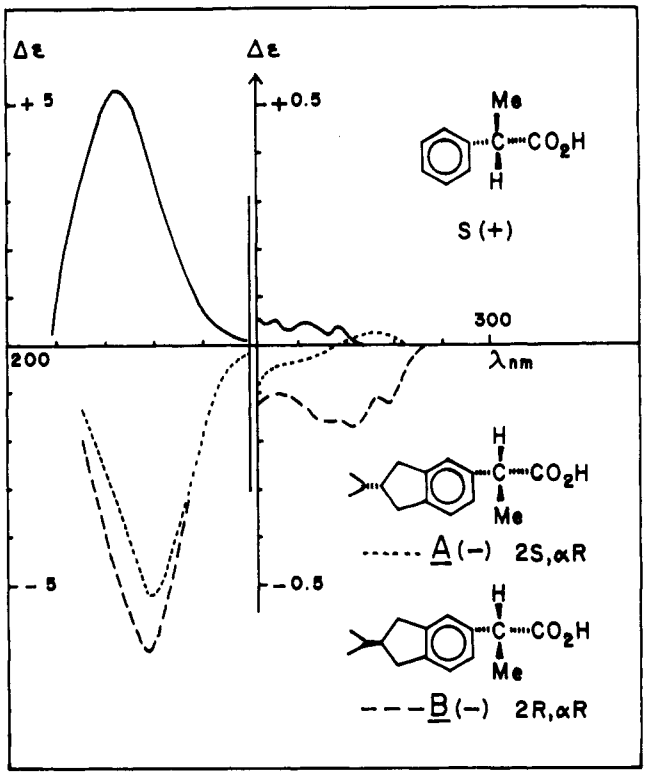


Figure 7. Circular dichroism of acids **7c**, (−)-(2*S*,α*R*) isomer A and (−)-(2*R*,α*R*) isomer B, and of (+)-(*S*)-hydratropic acid[8] in methanol (c 2, g/L).

extensive series of α-substituted phenylacetic acids.

In Figure 7 we give the CD curve of the diastereoisomers studied and also that of (*S*)-(+)-hydratropic acid, which is closely related to them. Comparison of these curves clearly permits the 2*R*,α*S* configuration to be attributed to the A (+) acid and the 2*S*,α*S* configuration to the B (+) acid.

Pharmacological Activity of Substituted Indanacetic Acids. The antiinflammatory activity of the compounds described in this paper was studied on carrageenan edema,[9] the analgesic activity on the antagonism of writhings produced by phenylbenzoquinone,[10] and the ulcerogenic activity by grading from 0 to 3 the intensity of gastric ulcers in the fasting rat treated 6 h earlier. The compounds were administered by the oral route, in a 1% w/v arabic gum vehicle.

The 50% effective doses (ED_{50}) and their 95% confidence limits were calculated by Bliss's method[11] (carrageenan edema; antagonism to phenylbenzoquinone). The 50% ulcerogenic dose (UD_{50}) was determined graphically.

The results (Table II) show, in the first place, that the propionic acids **7** are more active than the corresponding acetic acids **9** and that, so far as concerns substitution in position 2, the 2-isopropyl and 2-ethyl derivatives are better than 2-methyl but not significantly different from each other.

In regard to the relationships between the stereochemistry and, in particular, the absolute configuration of the arylpropionic acids and their antiinflammatory properties, it is known that the following alternative may exist: either the stereochemistry has no influence and the enantiomers have the same activity [as, for example, for *p*-isobutyl- and *m*-phenoxyhydratropic acids (ibuprofen and fenoprofen)] or it is decisive [as, for example, for α-(6-methoxy-2-naphthyl)propionic acid (naproxen)] and in that particular case the more potent antipode has the *S* configuration.[12] (It has been shown for ibuprofen that the *R* isomer is metabolically converted to the *S* isomer.[13])

In view of the difficulties of separation that we have seen in the case of 2-isopropyl-α-methylindan-5-acetic acid, it was possible to perform our comparative trials only on the racemic mixture of the two diastereoisomers, on mixtures (in approximately equal parts) of the resolved acids A and B of the same sign, and on the acid A (+). We found no significant difference in activity (ED_{50}) between these various samples.

These results permit a choice between two interpretations: (a) either the four pure isomers have the same activity or (b) in each racemic diastereoisomer a single antipode has the whole of the activity, with the following alternatives—A (+) is active and B (+) is inactive or A (−) is active and B (−) is inactive. This latter hypothesis must obviously be rejected, since the activity of pure A (+) is not twice that of its equimolecular mixture with B (+).

The four isomers are therefore biologically equivalent.

Experimental Section

Melting points were determined either in capillary tubes using a Dr. Tottoli apparatus and applying no correction or with a Perkin-Elmer differential scanning calorimeter (DSC2) with simultaneous determination of the sample purity from the shape of the melting peak. Routine IR and NMR spectra were consistent with the structures indicated. Analyses for elements indicated by the symbols were within ±0.4% of the calculated values. Satisfactory molecular weights of acids **7** and **9**, within ±2% of the theoretical values, were obtained by acidimetry. The purity of the compounds was checked by TLC on precoated silica gel plates (Merck F254) or by GC with a Hewlett-Packard 5830A gas chromatograph. Optical rotations were measured with a Perkin-Elmer 141 automatic polarimeter at 25 °C in EtOH (*c* 1%). CD data were determined using a Jouan dichrograph (model II), in MeOH (*c* 2, g/L), with 2- and 0.1-mm cells. All the organic solutions were dried over Na_2SO_4.

Method I (Scheme I). Ethyl 2,3-Dihydro-2-methyl-α-oxo-1*H*-indene-5-acetate (3a). A solution of **2a**[14] (66 g, 0.5 mol) and ethyloxalyl chloride (78.5 g, 0.57 mol) in CH_2Cl_2 (260 mL) was added dropwise (1 h) to a stirred suspension of $AlCl_3$ (116 g, 0.87 mol) in CH_2Cl_2 (260 mL), the reaction temperature being held below 5 °C by external cooling. The reaction mixture was then stirred at room temperature for 2 h, poured onto ice (2 kg), and acidified with concentrated HCl (pH 3). The aqueous layer was extracted once more with CH_2Cl_2 and the combined extracts were washed with brine, dried, and evaporated to give 110 g of **3a** in the form of an oil which was used directly without further purification.

2,3-Dihydro-2-methyl-α-oxo-1*H*-indene-5-acetic Acid (4a). A solution of crude **3a** (110 g, 0.47 mol) in EtOH (350 mL) was refluxed with NaOH (26 g) in H_2O (350 mL) for 2 h. The reaction mixture was cooled, diluted with H_2O (350 mL), acidified with 10% HCl at 0 °C, and extracted with ether. The extract was washed with H_2O, dried, and evaporated, yielding 98 g of **4a**, in the form of an oil which was used directly without further purification.

2,3-Dihydro-α-hydroxy-α,2-dimethyl-1*H*-indene-5-acetic Acid (5a). A solution of MeMgI in ether [prepared from Mg (36.6 g, 1.5 mol), MeI (115 mL, 1.85 mol), and ether (715 mL)] was added dropwise (1 h), with stirring, to an ice-cooled solution of crude acid **4a** (63 g, 0.29 mol) in ether (715 mL). The reaction mixture was then stirred at ambient temperature for 2 h, poured into ice, acidified with 10% HCl, and extracted with EtOAc. The organic layer was washed with H_2O, dried, and evaporated. The solid residue was washed with petroleum ether, giving 48 g of **5a** (68% overall yield from **2a**) in the form of white crystals, mp 97–100 °C.

2,3-Dihydro-2-methyl-α-methylene-1*H*-indene-5-acetic Acid (6a). A solution of **5a** (33 g, 0.15 mol) and concentrated H_2SO_4 (57 mL) in dioxane (1.05 L) was heated under reflux for 2 h, cooled, and poured onto ice. The resulting precipitate was collected, washed with H_2O, and dried to yield 29 g of **6a** (96%) in the form of light-colored crystals, mp 119 °C.

2,3-Dihydro-α,2-dimethyl-1*H*-indene-5-acetic Acid (7a) Sodium Salt (1:1 Mixture of Diastereoisomers). A solution of **6a** (29 g) in MeOH (200 mL) was hydrogenated at 50 atm and 80 °C in the presence of Raney Ni (10 g) for 7 h. After cooling, the catalyst was removed by filtration and the filtrate was evaporated to give the oily acid **7a**. This oil (14.6 g) was treated with a solution of EtONa in EtOH (prepared from 1.65 g of Na and 200 mL of EtOH). Evaporation of the solvent left a solid residue which was triturated with ether to give 13 g of the sodium salt of **7a** in the form of a white powder, mp 127–130 °C. Anal. ($C_{13}H_{15}NaO_2$) mol wt 226.25.

2,3-Dihydro-2-methyl-1*H*-indene-5-acetic Acid (9a). A mixture of **4a** (40 g, 0.2 mol) and hydrazine hydrate (80 mL) was boiled for 45 min and cooled to 70 °C. KOH (50 g, pellets) was added in portions and the mixture was refluxed for 1.5 h. After evaporation of the excess hydrazine hydrate under reduced pressure, the resulting solution was cooled and diluted with H_2O, and the neutral products were removed by extraction with $CHCl_3$. The aqueous layer was acidified at 0 °C with 10% HCl and extracted with petroleum ether. The organic extract was washed with H_2O, dried, and evaporated. Recrystallization of the residue from pentane afforded 26 g of **9a** (68%), mp 57–58 °C. Anal. ($C_{12}H_{14}O_2$) C, H; mol wt 190.24.

The same procedure was used to prepare the acids **7b–d** and **9b–d** via the following compounds. (1) From 2-ethylindan (**2b**):[15] **3b** (oil), **4b** (oil), **5b** (oil), **6b** (mp 88–91 °C), **9b** [mp 47–48 °C. Anal. ($C_{13}H_{16}O_2$) C, H; mol wt 204.27]. (2) From 2-isopropylindan (**2c**):[16] **3c** (oil), **4c** (mp 55–60 °C), **5c** (mp 140–143 °C), **6c** (mp 145–148 °C). (3) From 2-cyclohexylindan (**2d**): **3d** (oil), **4d** (mp 117–121 °C), **5d** (mp 142–144 °C), **6d** (mp 172–182 °C), **9d** [mp 128–132 °C. Anal. ($C_{17}H_{22}O_2$) C, H; mol wt 258.36], **7d** [mp 119–121 °C. Anal. ($C_{18}H_{24}O_2$) C, H; mol wt 272.39].

Method 2 (Scheme I). 1-(2-Ethyl-2,3-dihydro-1*H*-inden-5-yl)ethanone (12b). A solution of 2-ethylindan (**2b**)[15] (269 g, 1.84 mol) and acetic anhydride (200 mL) was added over 1 h to a stirred suspension of $AlCl_3$ (570 g, 4.3 mol), in CH_2Cl_2 (1.2 L), the reaction temperature being held below 35 °C by cooling. The mixture was then stirred for 3 h at room temperature and worked up as in the case of **3a**. Distillation of the crude oil gave the ketone **12b** (273 g, 79%), bp 120–130 °C (1 mm).

2-Ethyl-2,3-dihydro-1*H*-indene-5-ethanol (13b). KBH_4 (7 g, 0.13 mol) was added in small portions to a solution of **12b** (72 g, 0.38 mol) in MeOH (200 mL). After stirring at room temperature for 3 h the reaction mixture was concentrated under reduced pressure, ice was added, and the product was extracted with ether. The organic layer was washed with H_2O, dried, and evaporated to yield 72 g of **13b**, in the form of an oil which was used directly.

5-(1-Chloroethyl)-2-ethyl-2,3-dihydro-1*H*-indene (14b). To a solution of crude **13b** (72 g, 0.38 mol) in benzene (220 mL) was added thionyl chloride (55 mL) over a period of 2 h, with stirring which was continued at ambient temperature for 30 min. The mixture was then poured onto ice, the benzene layer was separated off, and the aqueous phase was extracted with ether. The combined extracts were washed with H_2O, 5% $NaHCO_3$ solution, and H_2O and dried. Evaporation of the solvents in vacuo left an oily residue (74 g) which was used directly.

2-Ethyl-2,3-dihydro-α-methyl-1*H*-indene-5-acetonitrile (15b). Compound **14b** (74 g, 0.35 mol) was added dropwise with stirring to a solution of NaCN (22.9 g, 0.47 mol) in HMPA (115 mL) heated to 90 °C. The mixture was kept at 90 °C for 5 h, cooled, diluted with ice water, and extracted with ether. The organic layer was washed with H_2O, dried, and evaporated, leaving an oily residue. Distillation gave 59 g of **15b** (85%), bp 140 °C (2 mm).

2-Ethyl-2,3-dihydro-α-methyl-1*H*-indene-5-acetic Acid (7b) (1:1 Mixture of Diastereoisomers). A solution of **15b** (59 g, 0.3 mol) in AcOH (95 mL), H_2SO_4 (95 mL), and H_2O (95 mL) was heated under reflux for 20 h, then cooled, and treated with ice. The product was taken up in ether. The organic layer was dried and evaporated, and the residue was recrystallized from pentane to yield 35 g of **7b** (54%), mp 47–48 °C, in the form of white crystals. Anal. ($C_{14}H_{18}O_2$) C, H; mol wt 218.30.

The acid **7c** was prepared similarly via the following compounds: **12c** (mp 40 °C), **13c** (mp <50 °C), **14c** (oil), **15c** [bp 128–134 °C (0.8 mm)].

Method 3 (Scheme I). Morpholinothioamide of 9c. A mixture of **12c** (prepared by the procedure described for **12b**) (100 g, 0.5 mol), sulfur (22.2 g), and morpholine (75 g) was heated for 12 h at 140 °C. The reaction mixture was then concentrated under reduced pressure and the residue triturated with EtOH (200 mL). The crystals were collected and washed with cold EtOH to give 95 g (63%) of the morpholinothioamide of **9c**, mp 120 °C.

2,3-Dihydro-2-(1-methylethyl)-1*H*-indene-5-acetic Acid (9c). A solution of the latter thioamide (95 g, 0.31 mol) in AcOH (125 mL) and concentrated HCl (175 mL) was heated under reflux for 18 h, poured onto ice, and extracted with ether. The organic layer was washed with H_2O, dried, and evaporated in vacuo. Recrystallization from petroleum ether afforded 63 g (93%) of **9c**, mp 81–83 °C. Anal. ($C_{14}H_{18}O_2$) C, H; mol wt 218.30.

9c Ethyl Ester. A solution of **9c** (85 g, 0.39 mol) and concentrated H_2SO_4 (6 mL) in EtOH (300 mL) was heated under reflux for 5 h and then concentrated under reduced pressure. The cooled residue was poured into ice water and extracted with ether. The organic layer was washed with H_2O, dried, evaporated, and distilled to give 84 g (88%) of the ester, bp 141–144 °C (1.5 mm).

Ethyl α-Ethoxycarbonyl-2,3-dihydro-2-(1-methylethyl)-1*H*-indene-5-acetate (10c). To a solution of the latter ester (54.1 g, 0.22 mol) in diethyl carbonate (355 mL), heated to 100 °C, was added dropwise a solution of NaOEt in EtOH [prepared from Na (6.45 g, 0.28 mol) and EtOH (162 mL)]. At the end of the addition the EtOH and the excess diethyl carbonate were distilled off until the distillation temperature reached 125 °C. The reaction mixture was then cooled, diluted with H_2O (125 mL) and AcOH (30 mL), and extracted with ether. The organic phase was washed with H_2O, dried, and evaporated to yield 68 g of **10c** in the form of an oil which was used directly.

2,3-Dihydro-α-methyl-2-(1-methylethyl)-1*H*-indene-5-acetic Acid (7c). To a stirred solution of EtONa in EtOH [prepared from Na (5.4 g, 0.23 mol) and EtOH (200 mL)] was added the latter ester (68.6 g). At the end of the addition the stirring was continued for 30 min and MeI (25 mL) was added. The mixture was then refluxed for 3 h, concentrated in vacuo, and refluxed for 5 h with a solution of 2.5 N NaOH (200 mL) in EtOH (100 mL). After concentration in vacuo, the mixture was diluted with H_2O and the neutral products were taken up in ether. The aqueous layer was acidified with dilute HCl and extracted with ether. Evaporation of the dried solvent left a residue of malonic acid (74 g), which was decarboxylated by heating at 160 °C in vacuo for 2 h. Recrystallization of the residue from hexane afforded 35 g of **7c** (69% overall yield from **9c** ethyl ester), mp 86–88 °C. Anal. ($C_{15}H_{20}O_2$) C, H; mol wt 232.32.

Methyl Esters 8. All the methyl esters were prepared by the addition of an ethereal solution of diazomethane to the acids **7**. The resulting solution was washed with dilute HCl, $NaHCO_3$ solution, and H_2O, dried, and evaporated to give the oily esters which were used directly for NMR diastereoisomeric analyses.

NMR Analysis of the Mixtures of Diastereoisomers 7. Increasing amounts of $Eu(dpm)_3$ were added to a solution of the methyl ester **8** (10–20 mg) in CCl_4 (0.5 mL). In most cases the estimation was based on the OMe signals.

Separation and Resolution of the Diastereoisomers 7c. 1:1 Mixture of (−) Isomers A and B. The mixture of 53.4 g (0.23 mol) of (±)-**7c** and 67.7 g (0.23 mol) of cinchonidine was dissolved in boiling EtOH (1 L). After being left to stand at room temperature for a few hours, the precipitated salts were collected and recrystallized four times from EtOH (salt/solvent ≃10% w/v) to give a first crop (24 g). Concentration of the mother liquors afforded additional crops (11 g): total yield 35 g (58%). This salt (28 mmol) was warmed up and stirred with 1 N HCl (50 mL) and the resulting oil crystallized on cooling. The crystals were collected, washed with H_2O, and dried: 15 g; $[\alpha]_{578}$ −55.0°.

The first mother liquors from crystallization of the salt were worked up as above to yield 25 g of (+)-**7c**, $[\alpha]_{578}$ +35°.

1:1 Mixture of (+) isomers A and B. The mixture of **7c** [$[\alpha]_{578}$ +35° (15.5 g, A/B = 1/1)] and of 13.8 g of L-acetonamine[5] was dissolved in hot EtOH (100 mL) and H_2O (50 mL). After being left to stand at room temperature for a few hours, 15 g of monohydrated salt was collected and dried at room temperature. The material was recrystallized three times from the same solvent (salt/solvent ≃5% w/v) to give a first crop (6.8 g). Concentration of the mother liquors afforded additional crops (5.9 g): total yield 12.7 g. This salt was worked up as above to yield 6.4 g of acid (+)-**7c**, $[\alpha]_{578}$ +55.5° (A/B = 1/1).

(+)-(2*R*,α*S*) Acid 7c (Isomer A). A hot solution of **7c** [$[\alpha]_{578}$ +36° (35.5 g, A/B = 1/1)] and (−)-α-methylbenzylamine (18.5 g) in EtOH (500 mL) was cooled and left at room temperature for a few hours. The salt was collected and recrystallized four or five times from EtOH (salt/solvent ≃10% w/v). Three crops (12.7 g) of the salt were collected and worked up as above to give 8.3 g of **7c**, $[\alpha]_{578}$ +55.0° (A/B = 7/3). Slow crystallization from cold hexane (≃5 °C) afforded two types of crystals: aggregates of small white needles (A/B = 6/4) and thicker prisms, bright and colorless (A/B > 9/1). These were picked out and recrystallized several times from aqueous MeOH to give pure (+)-A: 1.3 g; $[\alpha]_{578}$ +55.6°; mp 65 °C.

Crystal Data. This compound crystallizes in the orthorhombic system with the following direct parameters: a = 26.207, b = 11.802, and c = 8.755 Å; V = 2707.9 Å^3; D_c = 1.14 g/cm^3; space group $P2_12_12_1$, Z = 8 (two independent molecules). The intensities of 3210 independent reflections were measured on a Philips PW 1100 diffractometer, 1525 of them being greater than 3σ. A calculation of the reliability factor gave R = 0.058 over 1200 structure factors.

(−)-(2*S*,α*R*) Acid 7c (Isomer A). This compound was prepared as above, starting from **7c** [$[\alpha]_{578}$ −55° (19 g, A/B = 1/1)] and (+)-α-methylbenzylamine (9.9 g): yield 5.3 g of **7c**; $[\alpha]_{578}$ −56.0° (A/B = 7/3). Crystallizations as above afforded pure (−)-A: $[\alpha]_{578}$ −55.9°; mp 65.5 °C; CD λ, nm (Δε), 276 (+0.03), 229 (−5.2).

(−)-(2*R*,α*R*) Acid 7c (Isomer B). Acid (+)-A (1 g) was esterified with ethereal diazomethane and then boiled with NaOMe (40 mg) in MeOH (10 mL) for 6 h. NaOH (2 N, 10 mL) was added and refluxing was continued for 1 h. Evaporation of MeOH, acidification, and extraction with ether yielded 1 g (mp 90 °C; $[\alpha]_{578}$ 0°) of a 1/1 mixture of (+)-A and (−)-B. The resolution was performed exactly as above for (−)-**7c** with cinchonidine to give pure (−)-B: 130 mg; $[\alpha]_{578}$ −56.0°; mp 67 and 70.5 °C (polymorph); CD λ, nm (Δε), 278 (−0.13), 271 (−0.17), 263.5 (−0.16), 228.5 (−6.4).

(±) Isomer A. Equal weights of (+)- and (−)-A were mixed and recrystallized twice from hexane: mp 96.5 °C.

(±) Isomer B. This compound was prepared as above from (+)- and (−)-B and recrystallized once from hexane: mp 95 °C.

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Supplementary Material Available: Melting diagrams of binary mixtures of optically active and racemic diastereoisomers of **7c** (Figures 1–5) and NMR characteristics of the lanthanide ester **8** complexes (3 pages). Ordering information is given on any current masthead page.

References and Notes

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