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Enantiomerically Pure 2,2-Dibromocyclopropanecarboxylic Acids, Simple Chiral Building Blocks

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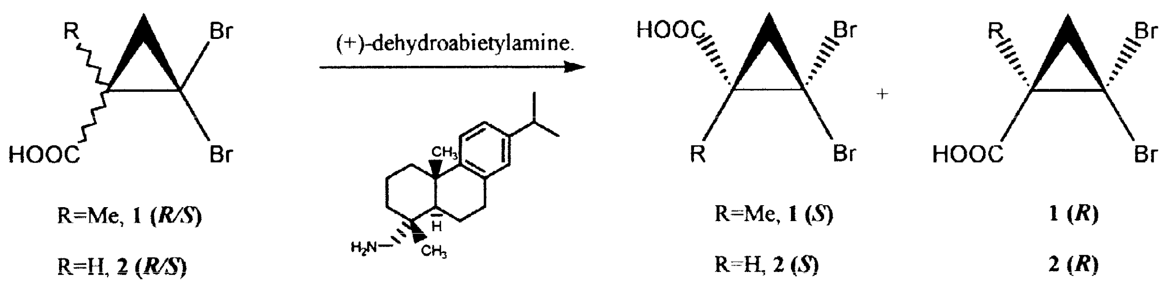
Abstract: Simple chiral building blocks 1-(*R*)- and 1-(*S*)-2,2-dibromocyclopropanecarboxylic acids and 2-(*R*)-bromo-1-(*S*)-cyclopropanecarboxylic acids and their 1-methyl analogues, have been obtained on a preparatively useful laboratory scale. © 1999 Elsevier Science Ltd. All rights reserved.

There are now many examples of the synthesis of single enantiomers of cyclopropanes, particularly in routes to important natural products and synthetic drugs,[1] either by introduction of the cyclopropane ring into starting materials taken from the chiral pool,[2] or, *e.g.* by processes such as cyclopropanation using a diazo-compound in the presence of a chiral catalyst.[3] Although many of these are very effective, there are relatively few reports of the preparation of single enantiomers of simple 1,1-dihalocyclopropanes and the applications of the many synthetically important reactions of such dihalides in asymmetric synthesis. We now report the resolution of two simple 2,2-dibromocyclopropanecarboxylic acids in procedures that may be readily applied on a large scale. In addition, we describe the application of a known reaction to convert optically pure acids **1** and **2**, into single enantiomers of the corresponding trans-2-bromocyclopropanecarboxylic acids **6** and **7**.



R=Me, **1** (***R/S***)
R=H, **2** (***R/S***)

R=Me, **1** (***S***)
R=H, **2** (***S***)

1 (***R***)
2 (***R***)

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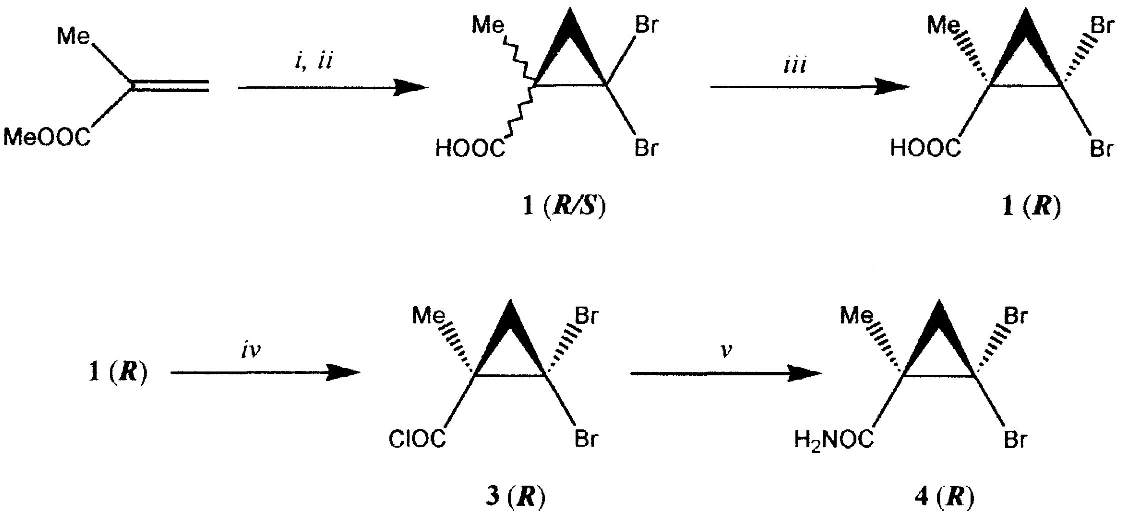
2,2-Dibromo-1-methylcyclopropanecarboxylic acid **1** (***R/S***), is readily prepared by the reaction of methyl methacrylate with bromoform and aqueous sodium hydroxide in the presence of a phase transfer catalyst;[4] subsequent acid hydrolysis leads to the formation of the desired product (**Scheme 1**):



Scheme 1: *i*) $CHBr_3$, NaOH(aq), TEAB, 15 °C, 6 hrs, 89 %; *ii*) HBr(aq), reflux, 4 hrs, 95 %; *iii*) (+)-dehydroabietylamine resolution; *iv*) $SOCl_2$, reflux, 2 hrs, 96 %; *v*) NH_3(aq), 1 hr, 86 %.

The acid **1** (***R/S***) was readily resolved by treatment with dehydroabietylamine in aqueous methanol,[5] the details of this procedure being presented below. The optical purity of the acid obtained in this way could be determined by gas liquid chromatography using a chiral column, which gave baseline resolution on both enantiomers of the corresponding methyl esters. The absolute stereochemistry of one enantiomer was determined unambiguously by X-ray crystallography on a single crystal of the amide **4** (***R***) ($[\alpha]_D^{20}$ + 41.6) derived from **1** (***R***), the structure of which is shown in *Fig. 1*.

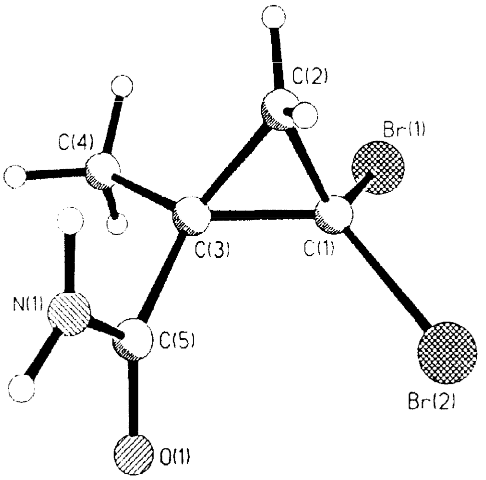
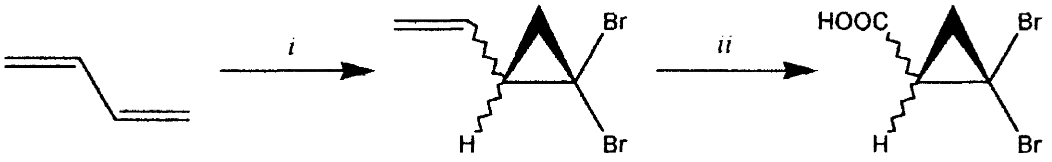


Fig. 1: Structure of one of the two independent molecules of 2,2-dibromo-1(*R*)-methylcyclopropanecarboxamide, showing the confirmed absolute stereochemistry. Molecules are linked together by N--H--O hydrogen bonds.

The analogous acid **2** (***R/S***) cannot be obtained efficiently by the dihalocyclopropanation of methyl acrylate under phase transfer conditions because of further reaction, presumably initiated by removal of the proton adjacent to the acid-group.[6] However, addition of dibromocarbene to 1,3-butadiene leads readily to the vinylcyclopropane **5** (***R/S***),[7] which upon oxidation with aqueous potassium permanganate yielded the acid **2** (***R/S***) in moderate yield (**Scheme 2**). This oxidation has previously been carried out on small scale using sodium periodate and ruthenium trichloride in 89 % yield.[8] Although this yield is slightly higher than that obtained with potassium permanganate, it is not the oxidant of choice due to its higher cost when carrying out reactions on a larger scale.

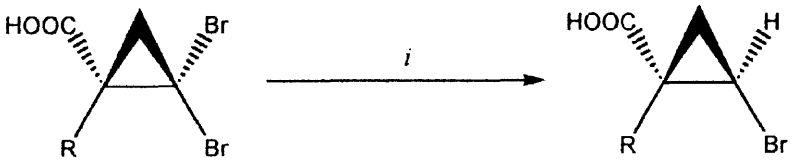


5 (***R/S***) **2** (***R/S***)

Scheme 2: *i*) $CHBr_3$, NaOH(aq), Pentane, -30 °C, 3 hrs, 76 %; *ii*) $KMnO_4$(aq), CH_2Cl_2, *n*-hexadecyltrimethyl-ammonium chloride, 20 °C, 48 hrs, 81 %.

Resolution of the acid **2** (***R/S***) in a similar manner to that above, led again to both enantiomers of the optically pure acid. Unfortunately the resolution of **2** (***R/S***) did not proceed with a similarly high recovery rate to that experienced for acid **1** (***R/S***). The recovery rate of each enantiomer (e.e. > 99 %) was around 20 % compared to a recovery rate of approximately 55 % of each enantiomer in the resolution of **1**. The absolute stereochemistry of **2** (***R***) was established through its use in the synthesis of (2*S*, 3*R*, 4*S*)-3,4-methanoproline,[9] a natural product obtained from *Aesculus parviflora*. The absolute stereochemistry of this was determined again by X-ray crystallography.[10]

The racemic dibromocyclopropane carboxylic acids **1** (***R/S***) and **2** (***R/S***) upon reaction with methyllithium are known to lead to the corresponding trans-2-bromocyclopropane carboxylic acids. The reaction is thought to proceed by an intramolecular transfer of the acid proton within the intermediate 2-bromo-2-lithiocyclopropane.[11]



R=Me, **1** (*S*) **6** (**1*S*, 2*R***)

R=H, **2** (*S*) **7** (**1*S*, 2*R***)

Scheme 3: *i*) 1.2 equiv. MeLi, diethyl ether, 0 °C, 90 mins, 98 %.

The application of this known reaction to the optically active **acids 1 (*S*) and 2 (*S*)** led to the controlled formation of a second chiral centre and hence the optically active **trans-monobromoacids 6 (2*R*, 1*S*) and 7 (2*R*, 1*S*)** ($[\alpha]_D^{25}$ −81.5 and -154.1° respectively) in high yield **(Scheme 3).**

The acids **1**, **2**, **6**,and **7** provide valuable precursors to a wide range of simple chiral cyclopropanes, for example the synthesis of (2*S*, 3*R*, 4*S*)-3,4-methanoproline.[9] Other applications are currently under examination.

EXPERIMENTAL SECTION

Reagents were obtained from commercial suppliers and were used without further purification unless stated. Dichloromethane was distilled over calcium hydride. Diethyl ether and tetrahydrofuran were distilled over sodium wire. Petroleum was either of boiling point 40 - 60 or 60 - 80 °C and was distilled. Reactions requiring anhydrous conditions were performed using oven dried glassware (250 °C) that was cooled under either dry nitrogen or argon; experiments were conducted under a positive atmosphere of one of these gases. Organic solutions were dried over anhydrous magnesium sulphate, and, unless stated, were evaporated at 14 mmHg. Yields quoted are for the purified compounds unless otherwise stated.

All new compounds were homogeneous by t.l.c. or by g.l.c. which was conducted using a Perkin-Elmer Model F17 F.I.D. on a capillary column (30 m x 0.32 mm id Phase, DB5 split ratio of 50:1) using nitrogen as carrier gas. Chiral g.l.c. was conducted using a 2,6-diamyl-3-trifluoroacetyl-γ-cyclodextrin fused silica column (40 m x 0.23 mm ID, film 0.12 mm), using helium as a carrier gas at 2 bar pressure (see acknowledgement). T.l.c. was performed using Aldrich silica gel 60 plates (F254). Compounds were visualised either by examination under an ultraviolet source or by exposure to iodine vapour. Column chromatography was conducted with Merck 7736 silica gel under medium pressure.

Melting points are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer as liquid films unless otherwise stated. Low resolution mass spectra were measured using a Finigan MAT 1020 spectrometer. Accurate mass measurements refer to ^{79}Br and ^{35}Cl isotopes unless stated and were carried out by the EPSRC Mass Spectroscopy Service (Swansea). Microanalysis was carried out on a Carlo Erba model 1106 CHN analyser. NMR spectra were recorded in $CDCl_3$ unless otherwise stated using a Bruker AC250 spectrometer at 250MHz (^{1}H) and 62.9MHz (^{13}C). ^{13}C spectra were broad band decoupled and in most cases corresponding DEPT spectra were also recorded. The results of DEPT spectra are quoted in the form of the signs + (corresponding to CH and CH_3 groups) and – (corresponding to CH_2 groups), signals which appear with no sign correspond to quaternary carbons.

Purification of (+)-dehydroabietylamine.

(+)-Dehydroabietylamine was obtained from Aldrich Chemical Co. as a mixture of high molecular weight primary amines. The purity was determined as 60 % by g.l.c. and the reagent was purified by crystallisation of its acetate[5] as outlined below.

A solution of glacial acetic acid (17 ml) in toluene (150 ml) was added dropwise over a period of 40 minutes to a cooled (0 °C) solution of (+)-dehydroabietylamine (70.00 g, 0.245 mol) in toluene (400 ml). The solution was stirred at 10 °C for 2 hours and the resulting precipitate collected under reduced pressure, washed with ice cold toluene (150 ml) and air dried. The white waxy solid was recrystallised from refluxing toluene (300 ml) to yield dehydroabietylamine acetate (55.25 g, 52 %) as fine white needle-shaped crystals, m.p. 141-3 °C, $[\alpha]_D^{21}$ + 31 (c 2.5, MeOH) (lit.,[5] m.p. 141 – 143.5 °C, $[\alpha]_D^{25}$ + 30.2).

Dehydroabietylamine acetate (50.00 g, 0.145 mol) was dissolved in warm deionised water (150 ml) and cooled to room temperature before adding 10 % aqueous sodium hydroxide (120 ml). The resulting solution was stirred for 1 hour before extracting the free amine into diethyl ether (250 ml). The organic solution was dried, filtered and reduced in volume under reduced pressure. Residual solvent was removed *in-vacuo* (0.1 mmHg) to yield (+)-dehydroabietylamine (39.65 g, 96 %) as a highly viscous yellow oil which crystallised slowly over an extended period (3 weeks), , m.p. 41.3 °C, $[\alpha]_D^{19}$ + 56.5 (c 2.55, pyridine) (lit.,[5] m.p. 41 °C, $[\alpha]_D^{22}$ + 55.6).

Resolution of 2,2-dibromo-1-methylcyclopropanecarboxylic acid, 1 (*R/S*).

A hot solution of purified dehydroabietylamine (5.73 g, 20 mmol) in methanol (100 ml) was added to a stirred hot solution of **1** (***R/S***) (20.50 g, 80 mmol) in aqueous methanol (water 20 ml, methanol 80 ml). The solution was stirred for approximately one minute until the first signs of crystallisation were observed. Stirring was then stopped and the solution allowed to cool to room temperature over a period of 3 hours to allow complete crystallisation. The crystals were collected *in vacuo*, washed with ice cold methanol (10 ml) and allowed to dry in the air. The product, an ammonium salt with the ratio 2:1 (acid:amine) was recovered as finely divided white crystalline needles (13.06 g, 16.2 mmol, 81 %). Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of 93 %. Further enantiomeric enrichment of the salt (up to 99 % e.e.) was carried out by recrystallisation of the salt from refluxing aqueous methanol (10 % H_2O, 90 % MeOH) (150 ml), and afforded fine white crystals (9.11 g, 11.3 mmol, 57 %), m.p. 209-210 °C (Found: C 45.1; H 5.5; N 1.6 %. Calculated for $C_{30}H_{43}Br_4NO_4$: C 44.97; H 5.41; N 1.75 %) which showed $[\alpha]_D^{20}$ -9.4 (c 0.472, MeOH) which showed δ_H: 0.87 (1 H, m), 0.99 (1 H, m), 1.08 (3 H, s), 1.19 (3 H, s), 1.23 (6 H, d, *J* 6.8), 1.40 (2 H, d, *J* 7.5), 1.5 (6 H, s), 1.6 – 1.8 (4 H, m), 2.30 (1 H, d broad, *J* 12.4), 2.46 (2 H, dd, *J* 9.6, 7.8), 2.75 –2.96 (5 H, m), 6.09 (6 H, s broad), 6.89 (1 H, s), 6.98 (1 H, d, *J* 8.2), 7.15 (1 H, d, *J* 8.2).

Treating the ammonium salt (9.11 g, 11.3 mmol), obtained as described above with 10 % aqueous sodium hydroxide solution (100 ml) and dichloromethane (100 ml) enabled the bulk regeneration of the optically active acid. The biphasic solution was stirred until all solids had dissolved and the resulting solution was then separated. The organic layer was extracted with 10 % aqueous sodium hydroxide solution (50 ml) and the combined aqueous fractions washed with dichloromethane (50 ml) [The combined organic layers were dried and evaporated enabling the efficient re-cycling of (+)-dehydroabietylamine]. The combined aqueous fractions were acidified with 20 % sulfuric acid and extracted with ethyl acetate (150 ml). The organic phase was dried, filtered and solvent removed to yield enantiomerically pure **1** ***(S)*** (5.59 g, 21.7 mmol, 97 %) as a white crystalline solid, m.p. 62-62.5 °C (Found: C 23.5; H 2.5 %. Calculated for $C_5H_6Br_2O_2$: C 23.29; H 2.34 %) which showed $[\alpha]_D^{20}$ -55.1 (c 1.015, $CHCl_3$), all other analytical data was identical to that of racemic material.[4] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of greater than 99 %.

The combined mother liquors were condensed to approximately half volume (175 ml) under reduced pressure and allowed to cool slowly to room temperature. After 12 hours, a further crop of crystals was collected *in vacuo*, washed with ice cold methanol (10 ml) and allowed to dry in the air. The crystals (2.21 g, 2.8 mmol, 14 %) were isolated as large white nodules and showed an enantiomeric excess of 60.2 %.

Enantiomerically enriched acid was regenerated from the mother liquor [which showed an enantiomeric excess of 47.8 % (+)] after evaporation of solvent under reduced pressure. Acid regeneration was carried out by treating the residual salt with 10 % aqueous sodium hydroxide solution (200 ml) and dichloromethane (200 ml). The biphasic solution was stirred until all solids had dissolved and the resulting solution was then separated. The organic layer was extracted with 10 % aqueous sodium hydroxide solution (50 ml) and the combined aqueous fractions washed with dichloromethane (50 ml). The combined aqueous fractions were acidified with 20 % sulfuric acid and extracted with ethyl acetate (250 ml). The organic phase was dried, filtered and solvent removed to yield enantiomerically enriched **1** (12.43 g, 48.3 mmol, 60 %) as a cream/white crystalline solid which showed an enantiomeric excess of 47.8 % (+) [The combined organic layers were dried and evaporated enabling the efficient recycling of (+)-dehydroabietylamine].

Further enantiomeric enrichment (up to 99 % e.e.) was carried out by slow recrystallisation of the acid (12.4 g, 48.2 mmol) from refluxing *n*-hexane (10 ml). After 15 hours at 5 °C, the crystals (6.51 g, 25.3 mmol, 53 %), which had an enantiomeric excess of 7 % (+) were removed. The mother liquor was evaporated to yield a colourless oil, which crystallised over night yielding **1** ***(R)*** (5.88 g, 22.8 mmol, 47 %) as a white crystalline solid, m.p. 62-62.5 °C (Found: C 23.5; H 2.5 %. Calculated for $C_5H_6Br_2O_2$: C 23.29; H 2.34 %), which showed $[\alpha]_D^{20}$ +54.7 (c 1.089, $CHCl_3$) (all other analytical data was identical to that of racemic material).[4] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of 99 %.

Methyl 2,2-dibromo-1(*S*)-methylcyclopropanecarboxylate.

An excess of ethereal diazomethane solution was added to acid **1** **(*S*)** (51.0 mg, 0.198 mmol) and the resulting solution was stirred at room temperature for 10 min. All volatiles were removed *in vacuo* to yield methyl 2,2-dibromo-1(*S*)-methylcyclopropanecarboxylate (53.2 mg, 99 %), as a viscous colourless oil, $[\alpha]_D^{20}$ -62.7 (c 1.060, $CHCl_3$) which showed a ^1H NMR spectrum identical to the racemate.[4]

Analysis by chiral g.l.c. showed an enantiomeric excess of > 99 % within the detection limits at baseline resolution. On the same chiral column the (*R*) enantiomer (prepared in the same way) gave a 99 % e.e., with a retention time of 19.4 min (compared to the (*S*) enantiomer with a retention time of 19.2 min).

2(*R*)-Bromo-1(*S*)-methylcyclopropane carboxylic acid, 6.

A 100 ml oven dried round bottomed flask was charged with **1** **(*S*)** (5.14 g, 20 mmol) in still dried diethyl ether (55 ml). The resulting solution was then cooled to 0 °C and a 1.5 M solution of MeLi in diethyl ether (20.0 ml, 30 mmol) was added dropwise over a period of 5 minutes. The golden yellow solution was then allowed to warm to room temperature and stirred for 1 hour.

Water (20 ml) was added to the reaction (dropwise at first) and the resulting solution was stirred for 10 minutes before being separated. The organic phase was extracted with water (20 ml) and the combined aqueous fractions acidified with 15 % aqueous sulfuric acid. The acidified aqueous phase was then extracted with ethyl acetate (100 ml), the organic extracts were dried, filtered and solvent removed *in vacuo* to yield **6** **(2*R*, 1*S*)** (3.29 g, 92 %) as a light golden semi-solid; $[\alpha]_D^{25}$ -81.5 (*c* 1.02 in $CHCl_3$) which showed ^1H NMR and IR spectra identical to those of the racemate,[12] δ_C: 16.39, 23.65, 25.72, 28.86, 179.90.

2,2-Dibromo-1(*R*)-methylcyclopropanecarbonyl chloride, 3 (*R*).[9]

Thionyl chloride (25 ml, 0.34 mol) was added to **(1, *R*)** (26.4 g, 0.1 mol) and the resulting solution was heated under reflux for 2 hrs. Excess thionyl chloride was removed by distillation and the residue was distilled at 39 – 40 °C at 0.8 mmHg to yield **3** **(*R*)** (27.2 g, 96%) as a pungent oil; $[\alpha]_D^{20}$ - 0.3 (c 1.104, $CHCl_3$) that showed δ_H: 1.77 (3H, s), 1.78 (1H, d, *J* 8.0), 2.52 (1H, d, *J* 8.0); δ_C: 21.76+, 34.37-, 42.97, 156.35.

2,2-Dibromo-1(*R*)-methylcyclopropanecarboxamide, 4 (*R*).

2,2-Dibromo-1(*R*)-methylcyclopropanecarbonyl chloride **3 (*R*)** (0.80 g, 2.89 mmol) was added slowly to a stirred 35 % solution of ammonia in water (5 ml). The reaction was stirred for 1 hr before adding water (20 ml) and extracting the product into chloroform (3 x 25 ml). The organic fractions were combined, dried and solvent was removed *in vacuo*. Recrystallisation of the residue from chloroform yielded **4(*R*)** (0.64 g, 86 %), as a white crystalline solid m.p. 157-158 °C, $[\alpha]_D^{20}$ +41.6 (c 1.014, $CHCl_3$), (Found: C 23.6, H 2.7, N 5.5. Calculated for $C_5H_7Br_2NO$: C 23.37, H 2.75, N 5.45) which showed δ_H: 1.57 (1H, d, J 7.8), 1.64 (3H, s), 2.39 (1H, d, J 7.8), 5.81 (2H, s); δ_C: (CD_3OD): 21.90, 31.72, 32.44, 36.56, 170.41; ν_{max}/cm^{-1}: 3376, 3211, 3080, 2992, 2976, 2931, 2783, 1658, 1453, 1432, 1401.

X-ray Crystallography of 2,2-dibromo-1(*R*)-methylcyclopropanecarboxamide, 4 (*R*).

Crystal data for $C_5H_7Br_2NO$, M_r = 256.94, monoclinic, space group $P2_1$, a = 9.812(3), b = 6.4409(16), c = 12.304(3) Å, β = 98.941(6)°, V = 768.1(4)Å^3, Z = 4, D_c = 2.222 g cm^{-3}, Mo Kα radiation, λ = 0.71073 Å, μ = 10.47 mm^{-1}, T = 160 K. From a crystal of size 0.65 x 0.55 x 0.03 mm on a Bruker AXS SMART CCD diffractometer, 8795 reflections were measured, giving 3441 unique data (θ < 28.2°, R_{int} = 0.160, corrected for absorption by face-indexed methods). The structure was solved by direct methods and refined on F^2 for all data with weighting $w^{-1} = \sigma^2(F_o^2) + (0.0452P)^2 + 9.9808P$, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were assigned anisotropic displacement parameters, and hydrogen atoms were included with riding model constraints. Final $R_w = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{½}$ = 0.1714, conventional R = 0.0652 on F values of 3281 reflections having $F_o^2 > 2\sigma(F_o^2)$, S = 1.101 on all F^2 values and 164 refined parameters. Residual difference map extremes (+1.95, -1.46 eÅ^3) are close to Br atoms. The enantiopole parameter[13] refined to 0.02(3), unambiguously identifying the absolute stereochemistry, which is the same for both independent molecules in the asymmetric unit. Programs were standard Bruker AXS control and integration software,[14] SHELXTL,[15] and local programs. Atomic co-ordinates, displacement parameters, and molecular geometry have been deposited at the Cambridge Crystallographic Data Centre.

2,2-Dibromo-1-vinylcyclopropane, 5 (*R/S*).

A 2 litre three necked flask equipped for addition and mechanical stirring at low temperature (dry ice condenser) was charged with a suspension of ground potassium *tert*-butoxide (61.6 g, 0.50 mol) in dry pentane (400 ml). The flask was cooled to -30 °C before adding condensed 1,3-butadiene (27.0 g, 0.50 mol) by syringe. The resulting solution was stirred vigorously while a solution of bromoform (131.0 g, 0.50 mol) in dry pentane (200 ml) was added dropwise over 90 minutes. The reaction mixture was stirred for a further 90 minutes at -30 °C, before being allowed to warm slowly to room temperature whilst stirring overnight. The reaction mixture was then cooled (0 °C) before adding water (500 ml) to the reaction vessel. The resulting solution was separated and the aqueous layer extracted with pentane (100 ml). The combined organic fractions were washed with brine, dried, filtered and pentane was removed *in vacuo*. The residue was distilled to yield the product, **5** (***R/S***) (82.1 g, 73 %) as a colourless liquid, b.p. 48-50 °C at 7 mmHg (lit.,[7] b.p. 69.5 °C at 26 mmHg) which showed δ_H: 1.58 (1 H, dd, *J* 7.7, 7.4), 1.97 (1 H, dd, *J* 10.2, 7.4), 2.30 (1 H, ddd, *J* 10.2, 8.0, 7.7), 5.29 (1 H, dd, *J* 9.9, 1.5), 5.34 (1 H, dd, *J* 17.0, 1.5), 5.57 (1 H, ddd, *J* 17.0, 9.9, 8.0); δ_C: 25.23, 29.39-, 34.16+, 118.77-, 135.81+.

2,2-Dibromocyclopropanecarboxylic acid, 2 (*R/S*).

A 5 litre flange flask equipped for mechanical stirring was charged with a solution of **5** (***R/S***) (74 g, 0.330 mol) and *n*-hexadecyltrimethylammonium chloride (3.2 g, 10 mmol) in dichloromethane (1 l) and water (1 l). The solution was then cooled to 0 °C whilst 9 M sulfuric acid solution (120 ml) was added in small portions over 30 minutes. Potassium permanganate (156.5 g, 990 mmol) was then added to the stirred solution in small portions ensuring that the reaction temperature did not rise above 5 °C. The reaction was then allowed to warm to room temperature and stirred for a further 24 hours.

The reaction vessel was cooled to 0 °C before adding 50 % aqueous sulfuric acid (400 ml). Sodium sulfate (100 g or as required to reduce manganese by-products) was then added in small portions. The resulting straw coloured solution was stirred for 10 minutes before being separated and the aqueous phase extracted with dichloromethane (800 ml). The combined organic fractions were washed with saturated brine solution and dried over anhydrous magnesium sulfate. The dry solution was filtered and solvent removed *in vacuo* to yield the crude product as a creamy residue. The residue was recrystallised from hexane-benzene (5:2) to yield **2** (***R/S***) (59.5 g, 74 %) as white crystals, m.p. 94-95 °C (lit.,[7,8] m.p. 95 °C) which showed δ_H: 2.09 (1 H, dd, *J* 9.6, 7.6), 2.19 (1 H, dd, *J* 7.7, 7.6), 2.64 (1 H, dd, *J* 9.6, 7.7), 10.65 (1 H, s); δ_C: 19.73, 28.66, 33.10, 173.20.

Resolution of 2,2-dibromocyclopropanecarboxylic acid, 2 (*R/S*).

A hot solution of (+)-dehydroabietylamine (11.2 g , 39 mmol) in methanol (30 ml) was added quickly to a hot solution of racemic **2** (***R/S***)-(76.5 g, 314 mmol) in methanol (185 ml) and water (400 ml). After 15 hrs at room temperature, the crystals formed were filtered from the mother liquor and washed with cold (0 °C) methanol - water (1:1, 50 ml). The crystals were dried *in vacuo* to yield a white crystalline solid (42.4 g). The crystals, an ammonium salt of the ratio 2:1 (acid:amine) was treated with aqueous sodium hydroxide solution (5 g, 125 mmol in 20 ml of deionised water) and chloroform (200 ml) to enable the regeneration of the optically enriched acid. The biphasic solution was stirred until all solids had dissolved and the resulting solution was then separated. The organic layer was extracted with 10 % aqueous sodium hydroxide solution (50 ml) and the combined aqueous fractions washed with chloroform (50 ml) [The combined organic layers were dried and evaporated enabling the efficient re-cycling of (+)-dehydroabietylamine]. The combined aqueous fractions were acidified with 20 % sulfuric acid (45 ml, 100 mmol) and extracted with chloroform (3 × 150 ml). The organic phase was dried, filtered and solvent removed to yield enantiomerically enriched **2** (*S*) (18.5 g, 76 mmol, 24 %) as a viscous colourless liquid, the corresponding methyl ester (prepared by reaction with excess ethereal diazomethane solution) showed an e.e. of 74.7 % e.e. by chiral g.l.c.

Enantiomeric enrichment of the acid was carried out by slow recrystallisation from refluxing *n*-hexane (60 ml). After 15 hours at 5 °C, the mother liquor was decanted from the crystals and evaporated to yield **2** (*S*) (12.6g, 52 mmol, 17 %) as a viscous colourless liquid. Slow crystallisation over a number of weeks yielded a white crystalline solid, m.p. 61–63 °C. Analysis of the corresponding methyl ester showed the solid to be 95.9 % e.e. by chiral g.l.c.

Further enrichment of **2** (*S*) to >99 % e.e. was carried out by recrystallisation of **2** (*S*) (5.00 g, 20.5 mmol) with (+)-dehydroabietylamine (0.74 g, 2.56 mmol) from aqueous methanol as highlighted in the first paragraph of this procedure. The product, an ammonium salt of the ratio 2:1 (acid:amine) was recovered as finely divided white crystalline needles (1.92 g), m.p. 180-182 °C, (Found: C 43.30, H 5.19, N 1.68. Calculated for $C_{28}H_{39}Br_4NO_4$: C 43.49, H 5.08, N 1.81) which showed δ_H: 0.89 (1 H, m), 0.96 (1 H, m), 1.06 (3 H, s), 1.22 (3 H, s), 1.22 (2 H, d, *J* 6.9), 1.25 – 1.77 (6 H, m), 1.84 (2 H, dd, *J* 9.6, 7.4), 1.98 (2 H, dd, *J* 7.8, 7.4), 2.30 (1 H, d broad, *J* 12.4), 2.46 (2 H, dd, *J* 9.6, 7.8), 2.75 –2.96 (5 H, m), 6.09 (6 H, s broad), 6.89 (1 H, s), 6.98 (1 H, d, *J* 8.2), 7.15 (1 H, d, *J* 8.2).

Subsequent acid regeneration as highlighted above yielded **2** (*S*) (1.18 g, 5 mmol) as white crystals, m.p. 62–64 °C, $[\alpha]_D^{20}$ –138.2 (c 0.982, $CHCl_3$), (Found: C 19.7, H 1.7. Calculated for $C_4H_4O_2Br_2$: C 19.70, H 1.65), all other analytical data was identical to that of racemic material.[7,8] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of greater than 99 %.

The original mother liquor was evaporated before adding chloroform (200 ml) and sodium hydroxide (12 g, 0.30 mol) in water (200 ml). The resulting two phase system was shaken until all the salt had dissolved. The aqueous layer was washed with chloroform (100 ml) and then acidified with 20 % aqueous sulfuric acid. The product was extracted into chloroform (3 x 200 ml) and the combined organic fractions were dried, filtered and solvent was removed to yield **2** (***R***), (55.4 g, 229 mmol) as a cream coloured solid with a 25.2 % e.e. (by chiral g.l.c. analysis of the corresponding methyl ester). This acid was dissolved in boiling hexane (150 ml) and the solution was left overnight at 5 °C. The supernatant solution was decanted from the crystals and evaporation of solvent afforded **2** (***R***) (10.1 g, 42 mmol, 14 %) as a viscous colourless liquid that crystallised over a number of weeks to yield a white crystalline solid, m.p. 61 - 63 °C, $[\alpha]_D^{20}$

+132.9 (c 1.104, $CHCl_3$), (Found: C 19.6, H 1.7. Calculated for $C_4H_4O_2Br_2$: C 19.70, H 1.65), all other analytical data was identical to that of racemic material.[7,8] Chiral g.l.c. analysis of the corresponding methyl ester (prepared on small scale by addition of an ethereal solution of diazomethane to regenerated acid) showed an enantiomeric excess of 96 %.

Methyl 2,2-dibromo-1(*R*)-cyclopropanecarboxylate.

An excess of ethereal diazomethane solution was added to acid **2 (*R*)** (54.3 mg, 0.223 mmol) and the resulting solution was stirred at room temperature for 10 min. All volatiles were removed *in vacuo* to yield methyl 2,2-dibromo-1(*R*)-cyclopropanecarboxylate (56.1 mg, 98 %), as a viscous colourless oil, $[\alpha]_D^{20}$ +112.6 (c 1.018, $CHCl_3$) which showed a ^1H NMR spectrum identical to that of racemic material.[5]

Analysis by chiral g.l.c. showed a 92.5 % e.e. within the detection limits at baseline resolution. On the same chiral column the (*S*) enantiomer (prepared in the same way) gave a 98 % e.e., with a retention time of 14.92 min (compared to the (*R*)-enantiomer with a retention time of 14.14 min).

2(*R*)-Bromo-1(*S*)-cyclopropanecarboxylic acid, 7.

A 100 ml oven dried round bottomed flask was charged with **2 (*S*)** (4.86 g, 20 mmol) in still dried diethyl ether (50 ml). The resulting solution was then cooled to 0 °C and a 1.5 M solution of MeLi in diethyl ether (20.0 ml, 30 mmol) was added dropwise over a period of 5 minutes. The golden brown solution was then allowed to warm to room temperature and stirred for 1 hour.

Water (20ml) was added to the reaction (dropwise at first) and the resulting solution was stirred for 10 minutes before being separated. The organic phase was extracted with water (20 ml) and the combined aqueous fractions acidified with 15 % aqueous sulfuric acid. The acidified aqueous phase was then extracted with ethyl acetate (100 ml) and the organic extracts were dried, filtered and solvent removed *in vacuo* to yield the crude product as a golden brown oil.

The crude product (3.15g) was decolourised by heating under reflux in acetone (20 ml) over activated charcoal (0.2 g) for 10 minutes, the solution was then cooled, filtered and solvent removed *in vacuo* to yield **7 (2*R*, 1*S*)**, 2(*R*)-bromo-1(*S*)-cyclopropanecarboxylic acid (2.95 g, 89 %) as a colourless oil, $[\alpha]_D^{25}$ -154.1 (*c* 1.03 in $CHCl_3$) which showed) which showed ^1H NMR and IR spectra identical to those of the racemate,[11] δ_C: 19.08-, 19.44+, 23.67-, 177.96.

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