Efficient Optical Resolution of *cis*-4-Methylcyclohex-4-ene-1,2-dicarboxylic Anhydride, *cis*-4-Methylcyclohex-4-ene-1,2-dicarboximide, and their Derivatives by Complexation with Optically Active Host Compounds Derived from Tartaric Acid

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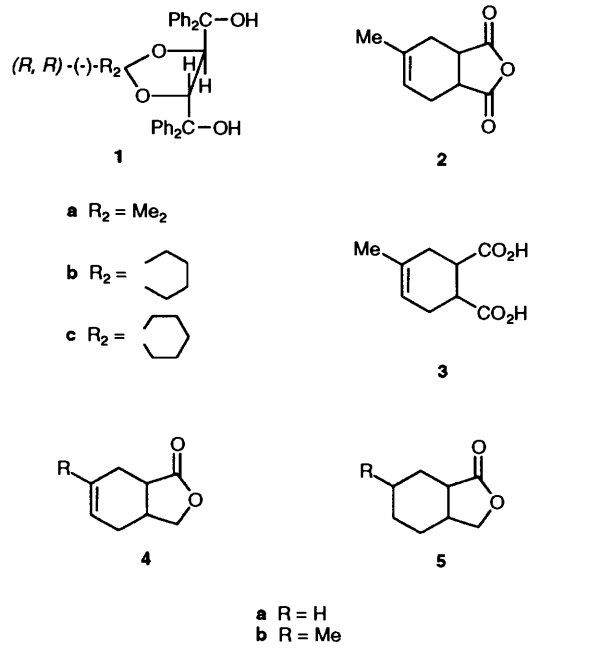
Optically pure enantiomers of *cis*-4-methylcyclohex-4-ene-1,2-dicarboxylic anhydrides, *cis*-4-methylcyclohex-4-ene-1,2-dicarboximides and 3-oxabicyclo[4.3.0]non-7-en-2-ones have been obtained by optical resolution through enantioselective inclusion complexation with optically active host compounds derived from tartaric acid. Kinetic resolution of cyclohex-4-ene-1,2-dicarboximides and cyclohexane-1,2-dicarboximides by way of enantioselective hydrolysis is also reported.

Optically pure enantiomers of the title compounds, important as key starting materials for the synthesis of various bioactive compounds, have been prepared by biological and enantioselective syntheses. These, however, are not always simple nor efficient. We now report a simple and efficient preparative method for these pure enantiomers by optical resolution through enantioselective complexation with optically active host compounds derived from tartaric acid. Kinetic resolution of some cyclohexane-1,2-dicarboximides and cyclohex-4-ene-1,2-dicarboximides in the solid state by a combination of enantioselective complexation and alkaline hydrolysis of uncomplexed enantiomer are also reported.

The three optically active host compounds used for the optical resolution were (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane **1a**,[1,2] (*R*,*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane **1b**,[3,4] and (*R*,*R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane **1c**.[1,2] These host compounds, easily derived from tartaric acid, are useful for the optical resolution of compounds such as bicyclo[2.2.1]heptanones,[5] bicyclo[2.2.2]octanones,[5] cyanohydrins,[6] glycerol acetals,[6] amino acid esters,[7] and hydroxy carboxylates,[7] through enantioselective complexation with their racemic compounds. The host **1a** has also been reported to be useful for the separation and purification of amines.[8]

Inclusion compounds were prepared by storing a solution of the host and racemic guest in the solvent described in the Experimental section. The initially formed inclusion compounds were purified by repeated recrystallisation from the same solvent. Melting points, IR spectral data, and analytical data for the purified inclusion compounds are shown in Table 1. Heating of the purified inclusion compounds *in vacuo* gave optically active guest compounds by distillation. For example, the optically pure (1*R*,2*R*)-(+)-enantiomer of *cis*-3-methylcyclohex-4-ene-1,2-dicarboxylic anhydride **2** was obtained in 52% yield by complexation with **1a** (Table 2). The optical purity of (+)-**2** was determined by conversion into the *N*-ethylimide derivative **6b**, the optical purity of which can easily be determined by HPLC using a column containing Chiralcel OJ as the optically active solid phase. Usually, preparation of optically pure **2** is not easy. For example, *trans*-4-methylcyclohex-4-ene-1,2-dicarboxylic acid **3** is resolved by a diastereoisomeric method using quinine to give optically pure (+)-**3** in 28% yield.[9] The enantioselective synthesis of the optically active **3** is more difficult. Diels–Alder reaction of 2-methylbuta-1,3-diene and dimenthyl fumarate gives (+)-**3** of 24% ee in 30% yield.[9]



3-Oxabicyclo[4.3.0]non-7-en-2-one **4a** and its 8-methyl derivative **4b** were resolved by complexation with **1b** instead of **1a**. Dihydro derivatives of **4a** and **4b** and **5a** and **5b**, respectively, were, however, resolved with **1c**. In these resolutions, efficiency was much higher for the 8-methyl derivatives, **4b** and **5b** (Table 2). Optically pure **4a** and **5a** have been prepared in good yields by biological oxidation of *cis*-1,2-dihydroxymethylcyclohexene and *cis*-1,2-dihydroxymethylcyclohexane, respectively.[10] Nevertheless, the resolution with **1** is very simple and convenient, and the efficient resolution of **4b** and **5b** is especially useful.

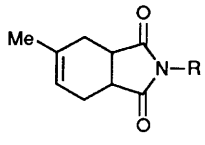
Preparation of optically active cyclohex-4-ene-1,2-dicarboximides **6** and cyclohexane-1,2-dicarboximides **7** has never been reported before. By the complexation with **1**, **6** and **7** were resolved efficiently. For example, **6a**, **6b** and **6c** were resolved with **1b**, **1c** and **1c**, respectively to give optically pure (+)-enantiomers in the yields shown in Table 2.

In the resolution of **6a**, for example, the host compounds were effective in the order of **1b** > **1a** > **1c**, even though **1c** also formed a complex with **6a**. There is a parallel relationship between the efficiency of the host in the resolution and the

Table 1 1:1 Inclusion compounds of **2**, **4**–**7** with **1**

Guest	Host	No. of recryst'ns[a]	Inclusion compound: Appearance	M.p. (°C)	IR ν_{max}(Nujol)/cm^{-1}	Analysis % Found (Calc.): C	H	N
2	**1a**	2	Prisms	118–121	3475, 3325 1840, 1775	$C_{40}H_{40}O_7$ 75.7 (75.93)	6.7 (6.37)	
4a	**1b**	2	Prisms	120–121	3280, 1760	$C_{41}H_{42}O_6$ 78.0 (78.07)	6.8 (6.71)	
4b	**1b**	2	Prisms	84–85	3270, 1765	$C_{42}H_{44}O_6$ 78.2 (78.23)	7.15 (6.88)	
5a	**1c**	2	Prisms	128–129	3290, 1760	$C_{42}H_{46}O_6$ 78.25 (77.99)	7.3 (7.17)	
5b	**1c**	2	Needles	113–116	3250, 1750	$C_{43}H_{48}O_6$ 78.3 (78.15)	7.25 (7.32)	
6a	**1a**	—	Prisms	122–124	3330, 1695	$C_{41}H_{43}NO_6$ 76.2 (76.25)	6.5 (6.71)	2.1 (2.17)
6a	**1b**	3	Prisms	144–145	3320, 1685	$C_{76}H_{77}NO_{10}$[c] 78.5 (78.39)	6.7 (6.67)	1.1 (1.20)
6a	**1c**	—	Needles	—[b]	3350, 1695	$C_{44}H_{47}NO_6$ 77.3 (77.05)	7.2 (6.91)	1.7 (2.04)
6b	**1c**	2	Needles	—[b]	3370, 1690	$C_{45}H_{49}NO_6$ 77.05 (77.23)	6.9 (7.06)	1.7 (2.00)
6c	**1c**	—	Needles	—[b]	3300, 1700	$C_{49}H_{49}NO_6$ 79.0 (78.69)	6.7 (6.00)	1.9 (1.87)
7a	**1c**	3	Needles	130	3560, 3370	$C_{44}H_{49}NO_6$ 76.5 (76.83)	7.4 (7.18)	2.0 (2.04)
7b	**1a**	3	Needles	—[b]	3380, 3270 1780, 1700	$C_{42}H_{47}NO_6$ 76.4 (76.22)	7.35 (7.16)	2.1 (2.12)
7b	**1b**	—	Prisms	—[b]	3350, 3250 1770, 1700	$C_{44}H_{49}NO_6$ 76.9 (79.85)	7.4 (7.46)	1.9 (2.12)
7c	**1b**	3	Prisms	114–115	3350, 3270 1770, 1700	$C_{45}H_{51}NO_6$ 76.9 (77.00)	7.4 (7.32)	2.15 (2.00)
7d	**1b**	3	Needles	140–142	3350, 3280 1770, 1700	$C_{45}H_{51}NO_6$ 76.8 (77.00)	7.4 (7.32)	2.0 (2.00)

[a] Inclusion complex formed initially was purified by repeated recrystallisation (number shown) from the solvent in which the inclusion complexation was carried out. [b] Did not show clear melting point. [c] Host–guest ratio is 2:1.



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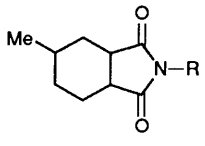
a R = Me
b R = Et
c R = Ph



7

a R = Me
b R = Et
c R = Pr
d R = Pr^i

stability of the host–guest inclusion complex. Dissociation energies of 1:1 inclusion complexes of (+)-**6a** with **1a**, **1b** and **1c** were determined by DSC measurement to be 39, 57 and 25 kJ mol^{-1}, respectively. These data show that the stronger the stabilization energy of the complex the more efficient the resolution.

Resolutions of **7a–d** with **1a–c** were all efficient and optically pure (+)-enantiomers were obtained in the yields shown in Table 2. For the resolution of **7b**, **1b** was more effective than **1a**.

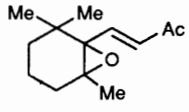
The optical resolution of some aliphatic compounds by complexation with (*S*)-1,1-diphenylbutane-1,3-diols, derived from lactic acid, has been reported, although the efficiency of the resolution was poor in most cases.[11]

All the host–guest inclusion complexations described above were carried out in solution. However, an enantioselective complexation occurs in the solid state when powdered optically active host and powdered racemic guest compound were mixed. For example, when a mixture of powdered **1c** and *rac*-β-ionone epoxide **8** was kept at room temperature for 1 day and the mixture then washed with hexane in order to remove uncomplexed (−)-**8** a 1:1 complex of **1c** and (+)-**8** of 88% ee in 24% yield was obtained. From the hexane solution, (−)-**8** of 36% ee was obtained in 36% yield.[12] By using this phenomenon, the

Table 2 Optical resolution of guest compounds by complexation with optically active host compounds

Guest	Host	Product			
		Yield (%)	Optical purity (% ee)[a]	$[\alpha]_D(c)$[b,c]	Optically active solid phase[d]
2	**1a**	52	100	+62 (0.45)	OJ
4a	**1b**	59	43	+40 (0.83)	OJ
4b	**1b**	56	100	+88 (0.70)	OJ
5a	**1c**	63	67	−28 (0.99)	OD
5b	**1c**	28	100	+64 (0.82)	OD
6a	**1a**	90	33	+18 (0.61)	As
6a	**1b**	16	100	−54 (0.47)	As
6a	**1c**	61	0	0	As
6b	**1c**	50	100	+51 (0.44)	OJ
6c	**1c**	38	100	+62 (0.47)	OJ
7a	**1c**	30	100	+97 (1.0)	OD
7b	**1a**	26	100	+97 (1.1)	As
7b	**1b**	63	100	+97 (0.90)	As
7c	**1b**	19	98	+88 (0.68)	As
7d	**1b**	40	98	+91 (0.88)	As

[a] Optical purities were determined by HPLC using a column containing the optically active solid phase shown in this table. [b] All $[\alpha]_D$ values were measured in MeOH. [c] In units of 10^{-1} deg cm^2 g^{-1}. [d] OJ, OD and As mean Chiralcel OJ, Chiralcel OD and Chiralpak As of Daicel Chemical Industries Ltd., respectively.



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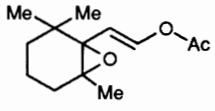

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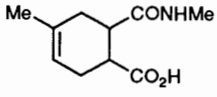

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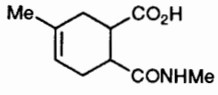

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kinetic resolution of **8** can also be carried out in the solid state. For example, a mixture of powdered **1c** and *rac*-**8** when further mixed with powdered *m*-chloroperbenzoic acid gave the Baeyer–Villiger oxidation product (−)-**9** of 72% ee (33% yield) together with a 1:1 complex of **1c** with (+)-**8** of 66% ee (43% yield).[12] In this experiment, uncomplexed (−)-**8** is oxidized to (−)-**9** faster than (+)-**8** is oxidized in its complex with **1c**. It has been established that Baeyer–Villiger oxidations proceed much faster in the solid state than in solution.[13]

Kinetic resolution in the solid state can be applied to both compounds **6** and **7**. For example, powdered **1b** and oily *rac*-**6a** were well mixed in an agate pestle and mortar for 1 h, and then further mixed with powdered KOH. After the mixture had been kept at room temperature for 30 min, it was washed with water to leave the crystalline 1:1 complex of **1b** and (+)-**6a**, which, when heated *in vacuo*, gave (+)-**6a** of 34% ee (83% yield) by distillation. From the KOH solution, hydrolysed product **10** and/or **11** was obtained. By the same procedure, **6b** and **7a–d** were also kinetically resolved quite efficiently (Table 3). In this case, enantioselective complexation and KOH-assisted hydrolysis of the imide in the solid state occur much faster than those in the case of **7**.

Table 3 Kinetic resolution of compounds **6** and **7** in the solid state

Guest	Host	Product		
		Yield (%)	Optical purity (% ee)[a]	$[\alpha]_D(c)$[b,c]
6a	**1b**	83	34	+18 (0.64)
6b	**1c**	96	27	+14 (0.82)
7a	**1c**	79	46	+44 (0.46)
7b	**1b**	75	54	+52 (0.63)
7c	**1b**	68	52	+47 (0.54)
7d	**1b**	64	50	+46 (0.61)

[a] Optical purities were determined by comparison of $[\alpha]_D$ values with those shown in Table 1. [b] In units of 10^{-1} deg cm^2 g^{-1}. [c] All $[\alpha]_D$ values were measured in MeOH.

Experimental

General Comments.—All optical purities were determined by HPLC using a column containing the optically active solid-phase mentioned individually, which is available from Daicel Chemical Industries, Ltd., Himeji, Japan. All $[\alpha]_D$ values were measured in MeOH and are recorded in units of 10^{-1} deg cm^2 g^{-1}. All melting points were taken in capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded at 60 MHz on a JEOL JNM-PMX 60 for solutions in $CDCl_3$ with tetramethylsilane as internal standard. *J* Values are given in Hz. Since inclusion complex dissociates to the host and guest components in solution, ^{1}H NMR spectra in $CDCl_3$ of inclusion crystals showed just the joint signals of the host and guest. In this Experimental section, ^{1}H NMR spectra of (+)-**6b**, (+)-**5b**, (+)-**6a** and (+)-**7a** are shown as representative examples.

Optical Resolution of cis-4-*Methylcyclohex*-4-*ene*-1,2-*dicarboxylic Anhydride* **2**.—A solution of **1a** (5.0 g, 21 mmol) and *rac*-**2** (3.6 g, 42 mmol) in ether–hexane (1:1) (60 cm^3) when kept at room temperature for 12 h gave colourless prisms of a 1:1 inclusion compound of **1a** and (+)-**2** (5.87 g, 85%). This, after two recrystallisations, gave the pure product (3.6 g, 53%), m.p. 118–121 °C, which when heated *in vacuo* (170–200 °C/5 mmHg) afforded (+)-**2** of 100% ee by distillation {0.93 g, 52% yield, $[\alpha]_D$ +62 (*c* 0.45)}. The optical purity of (+)-**2** was determined for the optically pure **6b** derived from the (+)-**2**. Treatment of the (+)-**2** first with 70% aqueous $EtNH_2$ in ether and then Ac_2O–AcONa gave optically pure (+)-**6b** (85%) {$[\alpha]_D$ +51 (*c* 1.04)}. The optical purity of the (+)-**6b** was determined by using Chiraicel OJ with hexane–propan-2-ol (9:1) as solvent (flow rate: 1.0 cm^3 min^{-1}, detection: UV 230 nm, α: 1.05), (+)-

6b. δ_H 1.10 (t, *J* 7, 3 H), 1.70 (s, 3 H), 2.10–2.77 (m, 4 H), 2.90–3.17 (m, 2 H), 3.47 (q, *J* 7, 2 H) and 5.27–5.63 (m, 1 H).

Optical Resolution of cis-8-*Methyl*-3-*oxabicyclo*[4.3.0]*nonan*-2-*one* **5b**.—A solution of **1c** (2.0 g, 4.0 mmol) and *rac*-**5b** (1.22 g, 8.0 mmol) in ether–hexane (1:1) (40 cm^3) was kept at room temperature for 12 h to give colourless crystals (2.33 g, 93%), a 1:1 inclusion compound of **1c** and (+)-**5b**. This after two recrystallisations from ether–hexane (1:1) gave pure product (0.78 g, 30%), m.p. 113–116 °C which when heated *in vacuo* (170–200 °C/5 mmHg) afforded (+)-**5b** of 100% ee (0.17 g, 28%),{$[\alpha]_D$ +64 (*c* 0.82)}. The optical purity was determined by using Chiralcel OD with hexane–propan-2-ol (9:1) as solvent (flow rate: 1.0 cm^3 min^{-1}, detection: UV 220 nm, α: 1.07). (+)-**5b**: δ_H 0.90 (m, 3 H), 1.00–2.83 (m, 9 H) and 3.93–4.30 (m, 2 H). By similar method, **4a**, **4b** and **5a** were resolved (Table 2).

Optical Resolution of cis-4-*Methyl*-N-*methylcyclohex*-4-*ene*-1,2-*dicarboximide* **6a**.—A solution of **1b** (4.0 g, 8.0 mmol) and *rac*-**6a** (1.46 g, 8.0 mmol) in ether–hexane (1:1; 40 cm^3) was kept at room temperature for 12 h to give colourless prisms of a 2:1 inclusion compound of **1b** and (+)-**6a** (4.28 g, 88%). This after three recrystallisations from ether–hexane (1:1) gave pure product (2.09 g, 43%), m.p. 144–145 °C which when heated *in vacuo* (170–200 °C/5 mmHg) afforded (+)-**6a** of 100% ee (0.12 g, 16%), {$[\alpha]_D$ +54 (*c* 0.47)}. The optical purity was determined by using Chiralpack As with hexane–EtOH (95:5) as solvent (flow rate: 1.0 cm^3 min^{-1}, detection: UV 220 nm, α: 1.09). (+)-**6a**: δ_H 1.72 (s, 3 H), 2.13–2.67 (m, 4 H), 2.93 (s, 3 H), 2.97–3.23 (m, 2 H) and 5.33–5.67 (m, 1 H). By a similar method, **6b** and **6c** were resolved (Table 2).

Optical Resolution of cis,cis-4-*Methyl*-N-*methylcyclohexane*-1,2-*dicarboximide* **7a**.—A solution of **1c** (2.0 g, 4.0 mmol) and *rac*-**7a** (1.42 g, 8.0 mmol) in benzene–hexane (1:1; 40 cm^3) was kept at room temperature for 12 h to give as colourless crystals a 1:1 inclusion compound of **1c** and (+)-**7a** (2.53 g, 93%). This, after three recrystallisation from benzene–hexane (1:1) gave pure product (1.48 g, 54%), m.p. 130 °C which, when heated *in vacuo* (170–200 °C/5 mmHg) afforded (+)-**7a** of 100% ee (0.24 g, 34%), {$[\alpha]_D$ +97 (*c* 1.0)}. The optical purity was determined by using Chiralcel OD with hexane–propan-2-ol (9:1) as solvent (flow rate: 1.0 cm^3 min^{-1}, detection: UV 220 nm, α: 1.03). (+)-**7a**: δ_H 0.90 (m, 3 H), 1.00–2.50 (m, 7 H) and 2.67–3.10 (m, 2 H). By a similar method, **7b–d** were resolved (Table 2).

Kinetic Resolution of **6a**.—Compound **2b** (0.50 g, 1.0 mmol) and *rac*-**6a** (0.36 g, 2.0 mmol) were well mixed in an agate pestle and mortar for 1 h, after which powdered KOH (0.56 g, 10 mmol) was added to the mixture and mixing continued for 30 min. The reaction mixture was washed with water to leave a 1:1 inclusion complex of **2b** and (+)-**6a** (0.55 g, 88%) which when heated *in vacuo* gave (+)-**6a** of 34% ee (0.15 g, 83%), {$[\alpha]_D$ + 18 (*c* 0.64)}. The optical purity was determined by using Chiralpack As with hexane–EtOH (95:5) as solvent (flow rate: 1.0 cm^3 min^{-1}, detection: UV 220 nm, α: 1.09). From the KOH solution, a mixture **10** and **11** was obtained as crystals: ν_{max}(Nujol)/cm^{-1} 3350, 3200, 2300, 1680 and 1630. By a similar method, **6b** and **7a–d** were kinetically resolved (Table 3).

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