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A Simple Preparative Method for Optically Active Glycidic Esters

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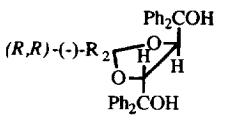
Abstract: Some optically active glycidic esters were prepared by resolution through inclusion complexation with a chiral host compound, *(R,R)*-(-)-trans-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane, and its derivatives.

Optically active glycidic esters are useful synthon for various biologically active substances such as leukotriene B_4,[1] kijanolide,[2] tetronolide,[2] and chlorothricolide.[2] Esterification of optically active glycidic acid which had been prepared from serine through a substitution of the amino group with bromine followed by dehydrobromination with KOH gives optically active glycidic esters.[3] Optically active glycidic acids can also be prepared by an asymmetric epoxidation[4] of allylic alcohols followed by oxidation with $RuCl_3/NaIO_4$.[5] However, glycidic acid is not very stable and is difficult to manipulate, and a special modifications are necessary for the esterification.[3]

We report herein a simple preparative method of optically active glycidic esters by optical resolution through inclusion complexation with an optically active host compound which has been derived from tartaric acid.

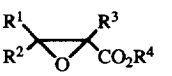
When a solution of *(R,R)*-(-)-trans-2,3-bis[hydroxydiphenylmethyl]-1,4-dioxaspiro-[4.4]nonane (**1a**)[6] (4.29 g, 8.71 mmol) and *rac*-ethyl 2,2-diethylglycidate (**2g**) (1.5 g, 8.71 mmol) in ether (7.5 ml)-hexane (2 ml) was kept at room temperature for 12 h, a 2:1 inclusion complex formed of **1a** and (+)-**2a** (3.18 g, 63% yield) as colorless prisms, which upon heating at 170 ℃/2 mmHg gave (+)-**2a** of 100% ee (0.47 g, 62% yield, $[\alpha]_D$ +37.4 (*c* 0.5, $CHCl_3$)). From the ether-hexane solution left after separation of the 2:1 inclusion crystal of **1a** and (+)-**2g**, (-)-**2g** of 45% ee (1.03 g, 137% yield, $[\alpha]_D$ -16.8 (*c* 0.5, $CHCl_3$)) was isolated. The enantiomeric excess was detemined by ^1H NMR spectrum measurement in the presence of the chiral shift reagent, (+)-Eu(hfc)$_3$. By the same inclusion complexation with **1a** and its analog **1b**[6] in ether, some other glycidic esters (**2a-f, 2h-j**) were resolved (Table 1). In most cases, the efficiency of the resolution is very good.



1

a: R_2=

b: R_2=



2

a: R^1=R^2=R^3=R^4=Me
b: R^1=R^2=R^3=Me; R^4=Et
c: R^1=R^2=R^4=Me; R^3=Et
d: R^1=R^2=Me; R^3=R^4=Et
e: R^1=R^2=R^4=Me; R^3=H
f: R^1=R^2=Me; R^3=H; R^4=Et
g: R^1=R^2=R^4=Et; R^3=H
h: R^1R^2= $(CH_2)_5$; R^3=H; R^4=Me
i: R^1R^2= $(CH_2)_5$; R^3=H; R^4=Et
e: R^1=R^3=R^4=Me; R^2=H

Table 1. Resolution of **2a-j** through inclusion complexation with **1** by recrystallization from solvent[a]

1	2	mp of 2:1 inclusion complex (°C)	product	yield (%)	optical purity[g] (% ee)
1a	**2a**	—[b,c]	(+)-**2a**	9	100
1a	**2b**	159-162[f]	(+)-**2b**	37	10
1b	**2b**	205-207[f]	(+)-**2b**	38	18
1a	**2c**	136-146[f]	(-)-**2c**	72	10
1a	**2d**	—[b,f]	(+)-**2d**	69	66
1b	**2d**	204-207[f]	(+)-**2d**	40	47
1a	**2e**	160-163[d]	(+)-**2e**	63	100
1b	**2f**	—[b,f]	(+)-**2f**	32	96
1a	**2g**	—[b,f]	(+)-**2g**	62	100
1b	**2g**	—[b,e]	(+)-**2g**	23	100
1a	**2h**	—[b,f]	(-)-**2h**	31	100
1b	**2h**	201-203[f]	(-)-**2h**	51	100
1b	**2i**	203-206[f]	(-)-**2i**	63	54
1a	**2j**	—[b,e]	(+)-**2j**	42	93

[a] Inclusion complexations with the host **1a** and **1b** were carried out in ether-hexane and toluene-hexane, respectively.

[b] Clear mp was not observed.

[c] Inclusion complex was purified by three recrystallizations from the same solvent as that used for inclusion complexation.

[d] Inclusion complex was purified by two recrystallizations from the same solvent as that used for inclusion complexation.

[e] Inclusion complex was purified by one recrystallization from the same solvent as that used for inclusion complexation.

[f] Inclusion complex was not purified by recrystallization.

[g] Enantiomeric excess was determined by mesurement of ^{1} NMR spectrum in the presence of chiral shift reagent, (+)-Eu(hfc)$_3$.

Table 2.Resolution of **2a-2j** through inclusion complexation with **1** by suspension in hexane or water

			hexane		H_2O	
1	**2**	product	yield (%)	optical purity[a] (% *ee*)	yield (%)	optical purity[a] (% ee)
1a	**2a**	(+)-**2a**	10	100	11	100
1a	**2b**	(+)-**2b**	—[b]	—	81	0
1b	**2b**	(+)-**2b**	—[b]	—	—[b]	—
1a	**2c**	(-)-**2c**	—[b]	—	74	0
1a	**2d**	(+)-**2d**	—[b]	—	—[b]	—
1b	**2d**	(+)-**2d**	72	43	90	45
1a	**2e**	(+)-**2e**	91	70	73	86
1b	**2f**	(+)-**2f**	54	100	78	100
1a	**2g**	(+)-**2g**	55	100	91	100
1b	**2g**	(+)-**2g**	95	100	95	100
1a	**2h**	(-)-**2h**	—[b]	—	46	90
1b	**2h**	(-)-**2h**	80	33	70	34
1b	**2i**	(-)-**2i**	70	15	89	30
1a	**2j**	(+)-**2j**	75	41	36	71

[a] Enantiomeric excess was determined by mesurement of ^{1} NMR spectrum in the presence of chiral shift reagent, (+)-Eu(hfc)$_3$.

[b] No inclusion complexation occurred.

The inclusion complexation of **1** and **2** can also be carried out by the suspension method in hexane or water.[7] For example, when a suspension of powdered **1a** (1.72 g, 3.48 mmol) and oily **2g** (0.6 g, 3.48 mmol) in hexane (4.3 ml) was stirred at room temperature for 24 h, a 2:1 inclusion complex of **1a** and (+)-**2g** was formed as colorless powder (1.77 g, 88% yield), which upon heating at 170 ℃/2 mmHg gave (+)-**2g** of 100% ee (0.17 g, 55% yield, $[\alpha]_D$ +35.9 (*c* 0.5, $CHCl_3$)). From the hexane solution left after separation of the 2:1 inclusion complex of **1a** and (+)-**2g**, (-)-**2g** of 40% ee (0.43 g, 145% yield, $[\alpha]_D$ -14.8 (*c* 0.5, $CHCl_3$)) was obtained. The suspension method can be applied to the resolution of some other glycidic esters (Table 2).

Resolution by a similar suspension method in water is also useful. When a suspension of powdered **1a** (1.72 g, 3.48 mmol) and oily **2g** (0.6 g, 3.48 mmol) in water (4.3 ml) containing hexadecyltrimethylammonium bromide (17.2 mg) as a surfactant was stirred at room temperature for 24 h, a 2:1 inclusion complex of **1a** and (+)-**2g** was obtained as colorless powder (1.83 g, 91% yield), which upon heating at 170 ℃/2 mmHg gave (+)-**2g** of 100% ee (0.27 g, 91% yield, $[\alpha]_D$ +34.7 (*c* 0.5, $CHCl_3$)). From the aqueous layer left after the separation of the 2:1 inclusion complex of **1a** and (+)-**2g**, (-)-**2g** of 85% ee (0.33 g, 109% yield, $[\alpha]_D$ -31.2 (*c* 0.5, $CHCl_3$)) was obtained by distillation. The suspension method in water is also applicable to the resolution of some other glycidic esters (Table 2).

A rather simple resolution method by fractional distillation in the presence of chiral host compound[7] is also available to glycidic esters. Heating of a mixture of powdered **1a** (1 g, 2.03 mmol) and oily **2g** (0.36 g, 2.03 mmol) at 80 ℃/2 mmHg gave (-)-**2g** of 51% ee (0.23 g, 129% yield, $[\alpha]_D$ -18.9 (*c* 0.5, $CHCl_3$)). Further heating at 170 ℃/2 mmHg of the residue left after distillation of (-)-**2g** gave (+)-**2g** of 92% ee (0.13 g, 74% yield, $[\alpha]_D$ +34.2 (*c* 0.52, $CHCl_3$)). Since (+)-**2g** forms an inclusion complex with **1a** by mixing **1a** and *rac*-**2g**, the uncomplexed (-)-**2g** evaporates at relatively low temperature and the complexed (+)-**2g** evaporates at higher temperature.

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