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EFFICIENT OPTICAL RESOLUTION OF SOME KEY COMPOUNDS OF PROSTAGLANDIN SYNTHESIS

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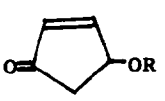
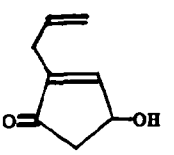
Abstract: 4-Hydroxycyclo-2-pentenone (**1a**), 2-allyl-4-hydroxycyclo-2-pentenone (**2**), bicyclo[3.2.0]-2-hepten-6-one (**4**), and bicyclo[4.2.0]-2-octen-7-one (**6**) were resolved efficiently by complexation with optically active host compound (**3**). Preparation of a new host compound (**3b**) was also described.

Although the optically active 4-hydroxycyclo-2-pentenone (**1a**) is a very important starting material of synthesis of prostaglandins,[1] it is not easy to obtain optically pure **1a** efficiently. Previously, we have reported an efficient resolution method of ester derivatives (**1b-d**) and tetrahydropyranyl ether derivative (**1e**) of **1a** by complexation with optically active 10,10'-dihydroxy-9,9'-biphenanthryl.[2] Recently, an efficient resolution of **1b** and some silyl ether derivatives of **1a** by HPLC on 1-phenylethylcarbamates of cellulose and amylose was also reported.[3] In these methods, however, one should prepare derivative of **1a** before resolution and hydrolyze the derivative after the resolution. We report very efficient direct resolution method of **1a** and its 2-allyl derivative (**2**) by complexation with (*S,S*)-(-)-1,4-bis[3-(*o*-chlorophenyl)-3-hydroxy-3-phenyl-1-propynyl]benzene (**3a**).[4]



a: R=H **d**: R=COPr
b: R=COMe **e**: R=
c: R=COEt

1

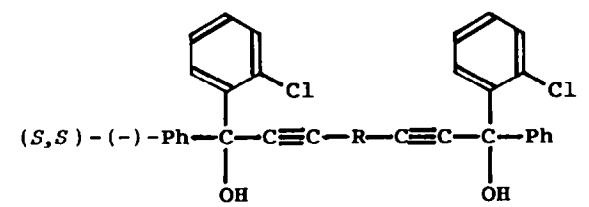


2

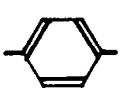
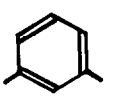
When a solution of **3a** (5.0 g, 8.94 mmol) and rac-**1a** (1.75 g, 17.9 mmol) in EtOH (10 ml) was kept at room temperature for 12 h, a 1:1:1 inclusion crystal of **3a**, (-)-**1a**, and EtOH was obtained as colorless psisms, after one recrystallization from EtOH, 3.63 g (57.7% yield, mp 70-75 °C). Heating of the crystal in vacuo gave (-)-**1a** of 100% ee (0.48 g, 54.9% yield, $[\alpha]_D$ -92.3 (*c* 0.63, MeOH)). When the inclusion complexation was carried out in toluene, a 1:2 inclusion crystal of **3a** and (+)-**1a** was obtained. After three recrystallizations from toluene, the inclusion crystal was heated in vacuo to give (+)-**1a** of 76.6% ee in 9.2% yield.

However, resolution of **2** was achieved efficiently both in toluene and EtOH. A solution of **3a** (3.0 g, 5.37 mmol) and rac-**2** (1.48 g, 10.7 mmol) in toluene (20 ml) was kept at room temperature for 12 h to give a 1:1 inclusion crystal of **3a** and (+)-**2** as colorless prisms, after one recrystallization from toluene, 1.83 g (38.9% yield, mp 118-120 °C). Heating of the crystal in vacuo gave (+)-**2** of 100% ee (0.35 g, 47.3% yield, $[\alpha]_D$ +35.3 (*c* 0.60, MeOH)). Result of the resolution is summarized in Table 1.

The optical purity of **1a** and **2** was determined by HPLC on the optically active solid phase, Chiralcel OC.[5]



3

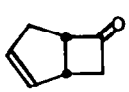
a: R=  b: R=  c: R=——

Optically active bicyclo[3.2.0]-2-hepten-6-one (**4**) and bicyclo[4.2.0]-2-octen-7-one (**6**) are also important key compounds of the preparation of various prostaglandins via the lactones **5** and **7**, respectively.[6] The most successful preparative method of the optically pure **4** and **5** is a biological resolution of **4** and a Baeyer-Villiger oxidation of the resolved **4**.[7] We have also reported optical resolution of **5** and **7** by complexation with (*S,S*)-(-)-1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (**3c**)[8] which gives optically pure (+)-**5** (10% yield) and (+)-**7** (10% yield), respectively.[9] Nevertheless, all these are not very efficient and not very convenient method. We now report very efficient resolution of **4** and **6** by

complexation with the new optically active host, (*S,S*)-(-)-1,3-bis[3-(*o*-chlorophenyl)-3-hydroxy-3-phenyl-1-propynyl]benzene (**3b**).

When a solution of **3b** (3.0 g, 5.37 mmol) and rac-**4** (1.16 g, 10.7 mmol) in ether-hexane (1:1, 10 ml) was kept at room temperature for 6 h, a 1:1 inclusion crystal of **3b** and (-)-**4** was obtained as colorless prisms, after one recrystallization from ether-hexane (1:1), 1.06 g (29.6% yield, mp 100-102 °C). Heating of the crystal in vacuo gave (-)-**4** of 100% ee (0.15 g, 25.9% yield, $[\alpha]_D$ -35.1 (*c* 0.69, MeOH)). By similar method, **6** was also resolved efficiently. When a solution of **3b** (3.0 g, 5.37 mmol) and rac-**6** (1.31 g, 10.7 mmol) in ether-hexane (1:1, 20 ml) was kept at room temperature for 48 h, a 1:1 inclusion crystal of **3b** and (+)-**6** was obtained as colorless needles, after one recrystallization from ether-hexane (1:1), 1.13 g (30.9% yield, mp 95-97 °C). Heating of the crystal in vacuo gave (+)-**6** of 100% ee (0.19 g, 29.0% yield, $[\alpha]_D$ -155 (*c* 0.30, MeOH)). The resolution of **4** and **6** was not achieved efficiently by complexation with **3a**. Result of the optical resolution of **4** and **6** is summarized in Table 1.

The optical purity of **4** and **6** was determined by HPLC on the optically active solid phase, Chiralcel OB.[4]



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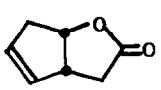

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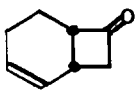

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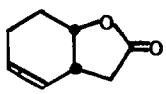

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Table 1. Optical resolution of guest compounds **1a**, **2**, **4**, and **6** by complexation with host compounds **3a** and **3b**

Host	Guest	Solvent of complexation	Result of resolution		
			Product	Optical purity (% ee)	Yield (%)
3a	**1a**	EtOH	(-)-**1a**	100	54.9
3a	**2**	toluene	(+)-**2**	100	47.3
3b	**4**	ether-hexane (1:1)	(-)-**4**	100	25.9
3b	**6**	ether-hexane (1:1)	(+)-**6**	100	29.0

The new optically active host compound **3b** ($[\alpha]_D$ -95.2 (*c* 1.0, MeOH)) was prepared in 74.6% yield from optically pure 1-(*o*-chlorophenyl)-1-phenyl-3-propyn-1-ol[10] and *m*-dibromobenzene in the presence of $PdCl_2(PPh_3)_2$ and Et_3N, by the similar procedure applied for the preparation of **3a**.[4]

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References and Notes.

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