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Resolution of 4-Hydroxy-2-cyclopentenone Derivatives by HPLC on Cellulose Triphenylcarbamate Derivatives[1)]

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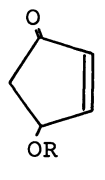
Trialkylsilyl ethers of 4-hydroxy-2-cyclopentenone, which are the key compounds for the syntheses of prostaglandins, were completely resolved on chiral HPLC columns packed with cellulose triphenylcarbamate derivatives.

Optically active 4-hydroxy-2-cyclopentenone (**1a**) and its derivatives (**1b**-**j**) are important building blocks of enormous utility for the syntheses of prostaglandins,[2)] and various synthetic methods including enzymatic hydrolysis and asymmetric synthesis have been reported.[2,3)]

Here, we wish to report the first direct optical resolution of 4-hydroxy-2-cyclopentenone derivatives, particularly silyl ethers, by HPLC on chiral stationary phases consisting of cellulose triphenylcarbamate derivatives (**2a**-**l**).[4,5)]

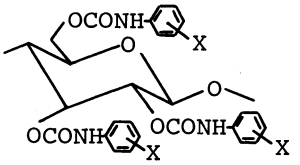
Chiral stationary phases were prepared by adsorbing the cellulose derivatives on silica gel,[4)] and were self-packed as HPLC columns (25 cm x 0.46 (i.d.) cm). Resolution was accomplished with a JASCO TRIROTAR-II chromatograph equipped with JASCO UVIDEC-III UV (flow cell length 1 mm) and DIP-181C polarimetric detectors



1

R =

a: H
b: $SiMe_3$
c: $SiEt_3$
d: $SiMe_2{}^tBu$
e: $SiMe_2Ph$
f: $SiMePh_2$
g: $SiPh_2{}^tBu$
h: $Si(MeO)Ph^tBu$
i: COMe
j: COPh



2

X =

a: 4-Et
b: 4-Me
c: H
d: 4-Br
e: 4-Cl
f: 4-F
g: $4-CF_3$
h: $3,4-Me_2$
i: $3,5-Me_2$
j: $3,4-Cl_2$
k: $3,5-Cl_2$
l: 4-Ph-N=N-

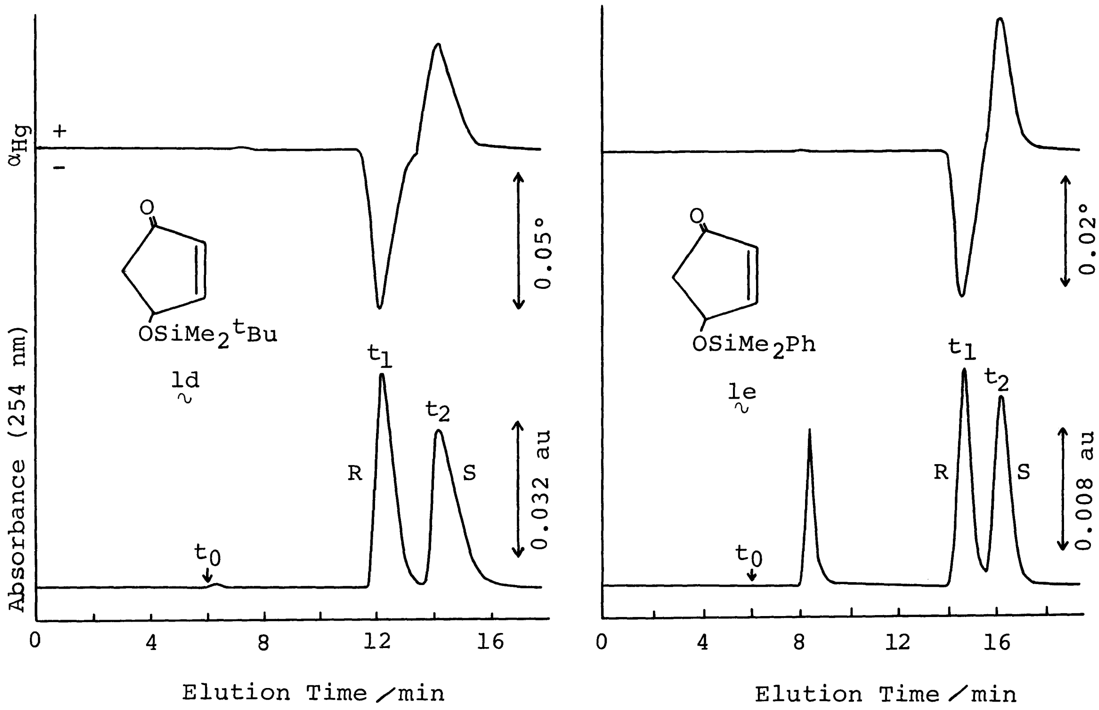


Fig. 1. Chromatograms of resolution of 1d and 1e on a cellulose triphenylcarbamate column (2c). (Eluent: hexane-2-propanol (98:2) for 1d, hexane-2-propanol (90:10) for 1e, sample: ≈0.5 mg for 1d, ≈0.1 mg for 1e)

(Hg, no filters, flow cell 5.0 cm x 0.3 (i.d.) cm) at 25 °C. Both detectors were connected in series. Non-retained time (t_0) was estimated with 1,3,5-tri-tert-butylbenzene.

Figure 1 shows the chromatograms of resolution of silyl ethers 1d and 1e on a cellulose triphenylcarbamate (2c) column. The ethers were sufficiently resolved into optical isomers. Polarimetric detection monitored with a mercury lamp without a filter showed that (−)-isomers eluted first. These (−)-isomers exhibited (+)-rotations at 589 nm and were proved to be (R)-isomers with optically active authentic samples of known absolute configuration. Three chromatographic parameters, capacity factor of the first-eluting isomer ($k_1' = (t_1 - t_0)/t_0$), separation factor (α = (capacity factor of second-eluting isomer)/ k_1'), and resolution factor (Rs = 2 x ($t_2 - t_1$)/(sum of band widths of two peaks)) were obtained as 1.03, 1.32, and 1.38, respectively, for 1d and 1.43, 1.17, and 1.30, respectively, for 1e from Fig. 1.

The results of resolution of 1a-j on 2c are summarized in Table 1. 4-Hydroxy-2-cyclopentenone 1a was not separated into two peaks. Acetate 1i and benzoate 1j were not suitable for resolution. (R)-Isomers of the silyl ethers were always less retained on the columns. Chiral recognition of 2c, which was evaluated by α, was higher for trialkylsilyl ethers 1b-d than for phenyl-containing silyl ether 1e-h. This suggests that the enhancement of electron density on ether oxygen may be desirable for resolution.

Table 1. Chromatographic data of the resolution of 1a-j on cellulose triphenylcarbamate (2c)a)

1	k_1'	α	Rs	1	k_1'	α	Rs
a	5.10 (S)b)	≃ 1		f	2.03 (R)b)	1.14	1.14
b	0.78 (R)	1.30	1.27	g	0.95 (R)	1.14	0.68
c	0.56 (R)	1.32	0.98	h	0.91 (R)	1.11	
d	0.48 (R)	1.31	1.07	i	4.13 (R)	1.04	
dc)	1.03 (R)	1.32	1.38	j	5.03 (R)	1.04	
e	1.43 (R)	1.17	1.30				

a) Eluent: hexane-2-propanol (90:10).

b) Absolute configuration of the first-eluted isomer.

c) Eluent: hexane-2-propanol (98:2).

Table 2. Resolution of 1d and 1e on cellulose triphenylcarbamate derivatives (2a-l)

		1da)			1eb)		
	2	k_1'	α	Rs	k_1'	α	Rs
a	4-Et	1.02 (R)c)	1.24	1.43	1.05 (R)	≃ 1	
b	4-Me	1.07 (R)	1.32	1.75	1.33 (R)	1.20	1.45
c	H	1.03 (R)	1.32	1.38	1.43 (R)	1.17	1.30
d	4-Br	1.73 (R)	1.20	1.29	1.80 (R)	1.11	0.89
e	4-Cl	1.54 (R)	1.17		1.51 (R)	1.07	
f	4-F	1.79 (R)	1.27	1.93	1.79 (R)	1.16	
g	4-CF_3	2.87 (R)	1.15	1.34	1.72 (R)	1.07	0.56
h	3,4-Me_2	0.68 (R)	1.32	1.20	1.13 (S)	1.33	1.32
i	3,5-Me_2	0.68 (R)	1.22	0.92	1.02 (S)	≃ 1	
j	3,4-Cl_2	1.73 (R)	1.15	1.23	1.93 (R)	1.11	0.84
k	3,5-Cl_2	1.32 (R)b)	1.13	0.88	2.37 (R)	1.08	0.73
l	4-Ph-N=N-	1.36 (R)	1.23	0.86	2.55 (R)	1.10	1.01

a) Eluent: hexane-2-propanol (98:2).

b) Eluent: hexane-2-propanol (90:10).

c) Absolute configuration of the first-eluted isomer.

Resolution of 1d and 1e was investigated on various cellulose triphenylcarbamate derivatives (Table 2). Although in most cases (R)-isomers eluted first, reversed elution order of enantiomers was observed in the resolution of 1e on dimethylphenylcarbamates 2h and 2i. Such a reversed elution on 2h and 2i has been obtained on several other racemic compounds.4b) Base-line separation of the both ethers was attained with the columns 2b and 2c.

On a preparative 2c column (25 x 2.0 (i.d.) cm), about 10 mg of 1d was completely resolved in a single injection by using hexane-2-propanol (98:2) as an eluent. The present chromatographic resolution will provide a convenient method of the preparation of optically pure silyl ethers of 4-hydroxy-2-cyclopentenone which are the key compounds for the very elegant prostaglandin synthesis found by Noyori and coworkers.[2)]

Most cellulose triphenylcarbamate derivatives showed rather low resolution for the alcohol **1a** and benzoate **1j**. Only **21**[6)] was able to resolve these compounds to some extents giving, $k_1' = 4.97$, $\alpha = 1.22$, Rs =0.63 for **1a** and $k_1' = 6.51$, $\alpha = 1.15$, Rs = 0.97 for **1j** (eluent; hexane-2-propanol (90:10)). Recently, **1a** was resolved on a cellulose triacetate column; $\alpha = 1.23$ was obtained under similar chromatographic conditions.[7)]

References

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5) Some of the chiral columns are commercially available from Daicel Chem. Ind. Ltd., 3-8-1 Kasumigaseki, Chiyoda-ku 100, Tokyo.

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