HETEROCYCLES. XXI.[1] LIQUID CHROMATOGRAPHIC OPTICAL RESOLUTION OF RACEMIC CHALCONE EPOXIDES AND FLAVANONOLS

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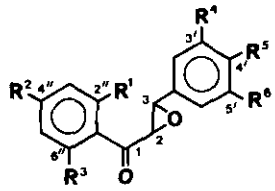
Abstract——Racemic chalcone epoxides and flavanonols have been separated into their enantiomers by hplc on a Chiralpack OT(+) column using methanol as the eluent.

We previously reported the efficient stereocontrolled synthesis of the racemic flavanonols[2a] and also the enantioselective synthesis of (+)- and (-)-flavanonols.[2b] Recently, it was shown that hplc can be employed for the optical resolution of racemates.[3] During our studies on the synthesis of natural products, we investigated the optical resolution of racemates by hplc. This paper is the first report on the optical resolution of racemic chalcone epoxides and flavanonols by hplc.

The optical resolution of the racemic chalcone epoxides 1, flavanonols 2 and their 3-acetates 3 has been examined by hplc on a reversed-phase Chiralpack OT(+) column using methanol as the eluent.

Table I shows the results obtained by hplc analysis of 1. The racemates 1a-1c, 1e and 1f were almost completely separated (the resolution factor ,Rs, were greater than 1). A simple correlation between the number of the methoxymethoxy groups on the aromatic rings and the Rs values was not observed. However it seems that the 3'-methoxymethoxy group increases the Rs values (compare 1b and 1c, and 1d and 1f), and the 4"-methoxyl group also influences strongly (compare 1e and others). Preparative hplc of 1d and 1f afforded their pure enantiomers, showing that the retention volumes of the (+)-enantiomers are larger than those of the (-)-enantiomers.

Table II shows the data for 2, in which the methoxyl groups on the aromatic



1a: R^1=OCH_2OMe
R^2=R^3=R^4=R^5=R^6=H

1b: R^1=R^2=R^5=OCH_2OMe
R^3=R^4=R^6=H

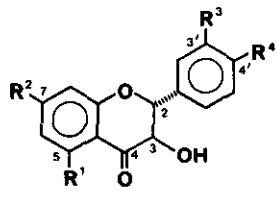
1c: R^1=R^2=R^4=R^5=OCH_2OMe
R^3=R^6=H

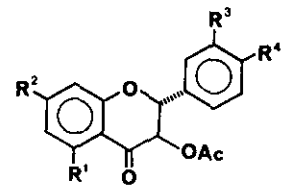
1d: R^1=R^2=R^3=R^5=OCH_2OMe
R^4=R^6=H

1e: R^1=R^3=R^4=R^5=OCH_2OMe
R^2=OMe R^6=H

1f: R^1=R^2=R^3=R^4=R^5=OCH_2OMe
R^6=H

1g: R^1=R^2=R^3=R^4=R^5=R^6
=OCH_2OMe





2a: R^1=R^2=R^3=R^4=H

2b: R^1=OMe
R^2=R^3=H R^4=OH

2c: R^1=R^4=OMe
R^2=R^3=H

2d: R^1=H
R^2=R^3=R^4=OMe

2e: R^1=R^2=R^4=OMe
R^3=H

2f: R^1=R^2=R^3=R^4=OMe

3a: R^1=R^2=R^3=R^4=H

3b: R^1=H
R^2=R^3=R^4=OMe

3c: R^1=R^2=R^4=OMe
R^3=H

3d: R^1=R^2=R^3=R^4=OMe

3e: R^1=R^4=OAc
R^2=R^3=H

3f: R^1=H
R^2=R^3=R^4=OAc

3g: R^1=R^2=R^4=OAc
R^3=H

Chart 1

Table I. Hplc Analysis of 1

Compd. No	k'[1] Less retained	More retained	α[2]	Rs[3]
1a	1.57	2.37	1.51	1.70
1b	1.01	1.34	1.33	1.27
1c	0.43	0.80	1.86	1.93
1d	0.87(-)	1.03(+)	1.18	0.88
1e	1.11	2.16	1.95	3.01
1f	1.14(-)	1.86(+)	1.63	2.00
1g	1.18	1.43	1.21	0.77

1) k'= capacity factor: (retained volume of enantiomer - void volume of column) / void volume of column. 2) α= k'2 / k'1 separation factor: (k' of more retained enantiomer / k' of less retained enantiomer). 3) Rs= resolution factor: 2 x (distance between the peaks of more and less retained enantiomer) / (sum of bandwidth of two peaks).

Table II. Hplc Analysis of 2

Compd. No	k' Less retained	More retained	α	Rs
2a	0.68	1.93	2.83	5.08
2b	0.47	0.69	1.46	0.94
2c	0.48	0.74	1.56	1.90
2d	0.44(+)	0.79(-)	1.82	1.44
2e	0.59(+)	1.00(-)	1.69	1.69
2f	0.61(+)	1.10(-)	1.80	1.92

Table III. Hplc Analysis of 3

Compd. No	k' Less retained	More retained	α	Rs
3a	1.51	2.33	1.54	2.52
3b	0.91(+)	1.25(-)	1.37	0.94
3c	1.17(+)	1.67(-)	1.43	1.68
3d	not separated (1.14)		----	----
3e	not separated (0.56)		----	----
3f	not separated (0.32)		----	----
3g	not separated (0.37)		----	----

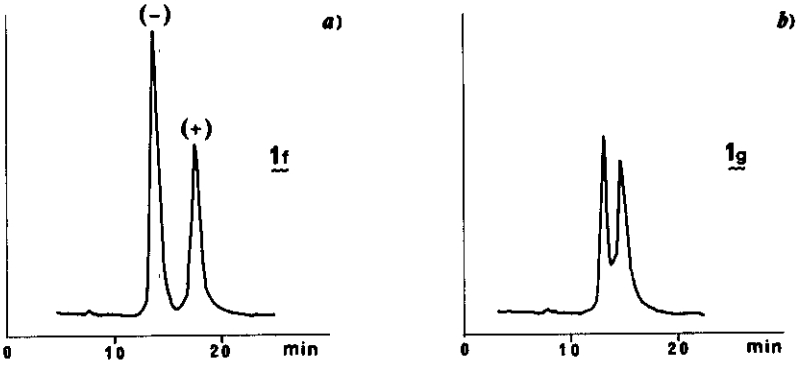


Fig. 1. a): 1f (Rs 2.00) , b): 1g (Rs 0.77)

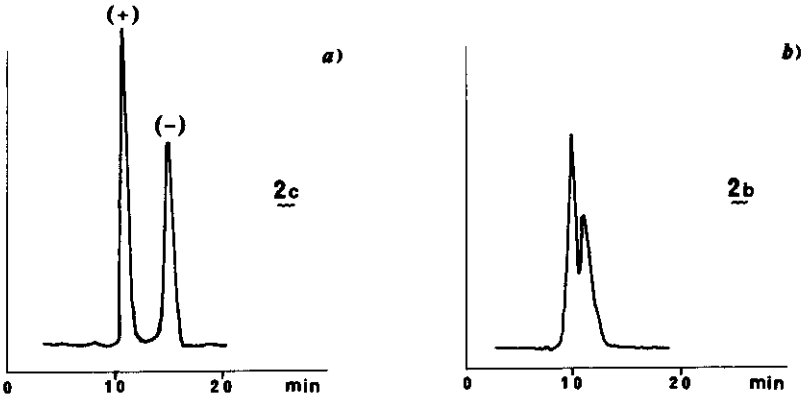


Fig. 2. a): 2c (Rs 1.69), b): 2b (Rs 0.77)

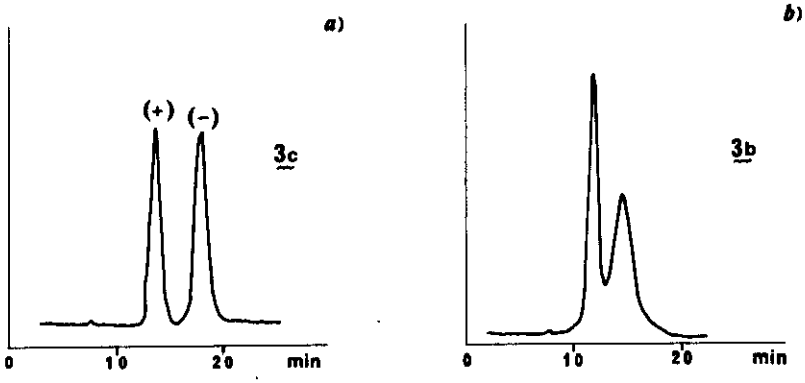


Fig. 3. a): 3c (Rs 1.68), b): 3b (Rs 0.94)

rings remarkably lower the Rs values (compare 2a and other). The racemates were almost completely resolved except 2b partially, Rs 0.94). Preparative hplc of 2d-2f provided their pure enantiomers, showing that the retention volumes of the (-)-enantiomers are larger than those of the (+)-enantiomers. The data for 3 are indicated in Table III. It can be seen that replacement of the 3-hydroxyl group by the acetoxy group lowers the Rs values (compare 3a and 2a, 3b and 2d, and 3d and 2f) except 3c (vs. 2e). Furthermore, the replacement of the methoxyl groups on the aromatic rings by the acetoxy groups made separation impossible (3e, 3f and 3g). The racemates 3a and 3c were almost completely resolved and 3b partially, and 3d was not absolutely. Preparative hplc of 3b and 3c gave their pure enantiomers, showing that the retention volumes of the (-)-enantiomers are larger than those of the (+)-enantiomers. Thus, it appears that hplc on a Chiralpack OT(+) column is an efficient and rapid tool in the optical resolution of the racemic chalcone epoxides and flavanonols as well as determination of optical purity of the enantiomers.

EXPERIMENTAL

Melting points were determined on a micro-stage apparatus and are uncorrected. Optical rotation was taken on a JASCO DPI-181 polarimeter. Spectral data were recorded on the following spectrometers: Ir, Hitachi 260-30; ^{1}H-Nmr, Varian EM-390 (90 MHz); Ms, JEOL JMS DX-300. Hplc was performed on a JASCO TRY ROTAR-V (pump), VL-614 (injector) and an UNIDEC-100-VI (detector). A reversed-phase column (25 x 0.46 cm i.d.) packed with Chiralpack OT(+) and 1%(w/v) injection solution were used for analytical hplc, and the mobile phase was methanol at a flow rate of 0.5 ml/min. A reversed-phase column (25 x 1 cm i.d.) was used for preparative hplc, and flow rate was 2.5 ml/min unless otherwise noted. The fractions containing the corresponding pure enantiomers were collected and concentrated *in vacuo*.

Preparation of Materials

The racemic chalcone epoxides and flavanonols used in this work are shown in Chart 1. The following compounds were already reported[2]: (±)-2,3-trans-2,3-epoxy-1-2"-methoxymethoxyphenyl-3-phenylpropanone (1a), (±)-tetrakis(methoxymethoxy)butein epoxide (1c), (±)-tetrakis(methoxymethoxy)isosalipurpol epoxide (1d), (±)-2,3-trans-2,3-epoxy-1-2",4",6"-tris(methoxymethoxy)phenyl-3-3',4'-

bis(methoxymethoxy)phenylpropanone (1f), (±)-2,3-trans-flavanonol (2a), (±)-2,3-trans-4'-hydroxy-5-methoxyflavanonol (2b), (±)-2,3-trans-5,4'-dimethoxyflavanonol (2c), (±)-fustin 7,3',4'-trimethyl ether (2d), (±)-aromadendrin 5,7,4'-trimethyl ether (2e), (±)-taxifolin 5,7,3',4'-tetramethyl ether (2f), (±)-2,3-trans-flavanonol 3-acetate (3a), (±)-2,3-trans-3,5,4'-triacetylflavanonol (3e), (±)-fustin 3,7,3',4'-tetraacetate (3f), (±)-aromadendrin 3,5,7,4'-tetraacetate (3g).

The unknown chalcone epoxides 1b, 1e and 1g, and flavanonol 3-acetates 3b-3d were prepared from the corresponding chalcones and flavanonols, respectively, according to the procedures described in the literature.[2]

(±)-2,3-trans-2,3-Epoxy-1-2",4"-bis(methoxymethoxy)phenyl-3-4'-methoxymethoxyphenylpropanone (1b)

Colorless needles of mp 95-96°C (EtOH). Yield, 90%. Ir ($CHCl_3$):1675 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 7.86 (1H, d, J 9.6 Hz, 6"-H), 7.30 (2H, d, J 9.0 Hz, 2'- and 6'-H's), 7.05 (2H, d, J 9.0 Hz, 3'- and 5'-H's), 6.78 (1H, d, J 2.1 Hz, 3"-H), 6.75 (1H, dd, J 9.6, 2.1 Hz, 5"-H), 5.17 (4H, s, CH_2 x 2), 4.88 (2H, s, CH_2), 4.28, 3.92 (each 1H, d, J 1.8 Hz, α- and β-H's), 3.45 (6H, s, CH_3 x 2), 3.13 (3H, s, CH_3). Ms Calcd for $C_{21}H_{24}O_8$: M, 404.147. Found m/z: M^+, 404.147.

(±)-2,3-trans-2,3-Epoxy-1-4"-methoxy-2",6"-bis(methoxymethoxy)phenyl-3-3',4'-bis(methoxymethoxy)phenylpropanone (1e)

A yellow oil. Yield, 86%. Ir ($CHCl_3$): 1675 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 7.12 (1H, d, J 8.4 Hz, 5'-H), 7.05 (1H, d, J 1.8 Hz, 2'-H), 6.88 (1H, dd, J 8.4, 1.8 Hz, 6'-H), 6.37 (2H, s, 3"- and 5"-H's), 5.17 (4H, s, CH_2 x 2), 5.09 (4H, s, CH_2 x 2), 3.91, 3.84 (each 1H, d, J 1.8 Hz, α- and β-H's), 3.76 (3H, s, CH_3), 3.46, 3.36 (each 6H, s, CH_3 x 4). Ms Calcd for $C_{24}H_{30}O_{11}$: M, 494.179. Found m/z: M^+, 494.179.

(±)-2,3-trans-2,3-Epoxy-1-2",4",6"-tris(methoxymethoxy)phenyl-3-3',4',5'-tris-(methoxymethoxy)phenylpropanone (1g)

Colorless needles of mp 64-65.5°C (EtOH). Yield, 98%. Ir ($CHCl_3$): 1695 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 6.75 (2H, s, 2'- and 6'-H's), 6.48 (2H, s, 3"- and

5"-H's), 5.14 (4H, s, CH_2 x 2), 5.11 (2H, s, CH_2), 5.08 (6H, s, CH_2 x 3), 3.89, 3.80 (each 1H, d, J 1.8 Hz, 2- and 3-H's), 3.60 (3H, s, CH_3), 3.45 (9H, s, CH_3 x 3), 3.34 (6H, s, CH_3 x 2). Ms Calcd for $C_{27}H_{36}O_{16}$: M, 584.211. Found m/z: M^+, 584.211.

(±)-Fustin 3-Acetyl-7,3',4'-trimethyl Ether (3b)

Colorless needles of mp 145-147°C (MeOH). Yield, 95%. Ir ($CHCl_3$): 1745 ($OCOCH_3$), 1690 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 7.87 (1H, d, J 9.0 Hz, 5-H), 7.04 (1H, dd, J 9.0, 2.5 Hz, 6'-H), 7.01 (1H, d, J 2.5 Hz, 2'-H), 6.87 (1H, d, J 9.0 Hz, 5'-H), 6.66 (1H, dd, J 9.0, 2.5 Hz, 6-H), 6.50 (1H, d, J 2.5 Hz, 8-H), 5.82 (1H, d, J 12.0 Hz, 2-H), 5.32 (1H, d, J 12.0 Hz, 3-H), 3.91 (6H, s, CH_3 x 2), 3.82 (3H, s, CH_3), 2.01 (3H, s, CH_3CO). Ms Calcd for $C_{20}H_{20}O_7$: M, 372.120. Found m/z: M^+, 372.121.

(±)-Aromadendrin 3-Acetyl-5,7,4'-trimethyl Ether (3c)

Colorless needles of mp 156-157°C (EtOH). Yield, 97%. Ir ($CHCl_3$): 1745 ($OCOCH_3$), 1690 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 7.41 (2H, d, J 9.0 Hz, 2'- and 6'-H's), 6.92 (2H, d, J 9.0 Hz, 3'- and 5'-H's), 6.11 (2H, s, 6- and 8-H's), 5.62 (1H, d, J 12.3 Hz, 2-H), 5.27 (1H, d, J 12.3 Hz, 3-H), 3.87 (3H, s, CH_3), 3.83 (6H, s, CH_3 x 2), 2.01 (3H, s, CH_3CO). Ms Calcd for $C_{20}H_{20}O_7$: M, 372.121. Found m/z: M^+, 372.118.

(±)-Taxifolin 3-Acetyl-5,7,3',4'-tetramethyl Ether (3d)

Colorless needles of mp 193-194°C (MeOH). Yield, 96%. Ir ($CHCl_3$): 1745 ($OCOCH_3$), 1690 cm^{-1} (C=O). ^{1}H-Nmr ($CDCl_3$) δ: 7.08 (1H, d, J 1.8 Hz, 2'-H), 7.02 (1H, dd, J 9.0, 1.8 Hz, 6'-H), 7.00 (2H, s, 6- and 8-H's), 6.90 (1H, d, J 9.0 Hz, 5'-H), 5.80 (1H, d, J 12.0 Hz, 2-H), 5.27 (1H, d, J 12.0 Hz, 3-H), 3.90 (6H, s, CH_3 x 2), 3.81 (3H, s, CH_3), 3.78 (3H, s, CH_3), 2.02 (3H, s, CH_3CO). Ms Calcd for $C_{21}H_{22}O_8$: M, 402.132. Found m/z: M^+, 402.131.

Preparative Hplc

(+)- and (-)-Tetrakis(methoxymethoxy)isosalipurpol Epoxide (1d)

A solution of (±)-1d (30.0 mg) in methanol (0.2 ml) was chromatographed. (+)-Enantiomer: A colorless oil. Rt 16.54 min. Yield, 13.2 mg (44%). Optical rotation $(\alpha)^{28}$(nm): +70.5°(589), +70.5°(577), +89.8°(546), +224.6°

(435)(c=0.6, $CHCl_3$), +931.1°(365)(c=0.0305, $CHCl_3$). Ms Calcd for $C_{23}H_{28}O_{10}$: M, 464.168. Found m/z: M^+, 464.168.

(-)-Enantiomer: A colorless oil. Rt 14.61 min. Yield, 14.3 mg (48%). Optical rotation $(\alpha)^{28}$(nm): -71.9°(589), -75.8°(577), -92.3°(546), -238.1°(435) (c=0.62, $CHCl_3$), -972.4°(365)(c=0.031, $CHCl_3$). Ms Calcd for $C_{23}H_{28}O_{10}$: M, 464.168. Found m/z: M^+, 464.169.

(+)- and (-)-2,3-trans-2,3-Epoxy-1-2",4",6"-tris(methoxymethoxy)phenyl-3-3',4'-bis(methoxymethoxy)phenylpropanone (1f)

A solution of (±)-1f (23.2 mg) in methanol (0.4 ml) was chromatographed.

(+)-Enantiomer: A colorless oil. Rt 15.49 min. Yield, 9.2 mg (40%). Optical rotation $(\alpha)^{30}$(nm): +62.4°(589), +65.9°(577), +79.6°(546), +208.3°(435) (c=0.45, $CHCl_3$), +888.2°(365)(c=0.023, $CHCl_3$). Ms Calcd for $C_{25}H_{32}O_{12}$: M, 524.189. Found m/z: M^+: 524.189.

(-)-Enantiomer: A colorless oil. Rt 13.83 min. Yield, 9.9 mg (43%). Optical rotation $(\alpha)^{30}$(nm): -64.8°(589), -69.5°(577), -84.8°(546), -222.4°(435) (c=0.42, $CHCl_3$), -961.9°(365)(c=0.021, $CHCl_3$). Ms Calcd for $C_{25}H_{32}O_{12}$: M, 524.189. Found m/z: M^+, 524.189.

(+)- and (-)-Fustin 7,3',4'-Trimethyl Ether (2d)

A solution of (±)-2d (15.8 mg) in methanol (0.2 ml) was chromatographed.

(+)-Enantiomer: *Colorless needles of mp* 146-148.5°C (EtOH). Rt 10.53 min. Yield, 6.4 mg (41%). Optical rotation $(\alpha)^{28}$(nm): +24.7°(589), +25.2°(577), +30.1°(546), +86.4°(435)(c=0.41, $CHCl_3$), +204.5°(365)(c=0.02, $CHCl_3$). Ms Calcd for $C_{18}H_{18}O_6$: M, 330.110. Found m/z: M^+, 330.110.

(-)-Enantiomer: Colorless needles of mp 145-148°C (EtOH). Rt 13.14 min. Yield, 7.8 mg (49%). Optical rotation $(\alpha)^{28}$(nm): -23.1°(589), -24.6°(577), -28.2°(546), -85.6°(435)(c=0.40,$CHCl_3$), -195.1°(365)(c=0.02, $CHCl_3$). Ms Calcd for $C_{18}H_{18}O_6$: M, 330.110. Found m/z: M^+, 330.110.

(+)- and (-)-Aromadendrin 5,7,4'-Trimethyl Ether (2e)

A solution of (±)-2e (20.0 mg) in methanol (0.1 ml) was chromatographed.

A flow rate was 1.5 ml/min.

(+)-Enantiomer: Colorless fine needles of mp 146.5-148°C (EtOH). Rt 21.20

min. Yield, 9.6 mg (48%). Optical rotation: $(\alpha)^{28}$(nm): +13.7°(589), +15.1° (577), +18.8°(546), +58.4°(435)(c=0.90, $CHCl_3$), +172.3°(365)(c=0.045, $CHCl_3$). Ms Calcd for $C_{18}H_{18}O_6$: M, 330.110. Found m/z: M^+, 330.109.

(-)-Enantiomer: Colorless fine needles of mp 148-149°C (EtOH). Rt 25.64 min. Yield, 9.2 mg (46%). Optical rotation $(\alpha)^{28}$(nm): -12.9°(589), -14.0°(577), -17.5°(546), -55.8°(435)(c=1.03, $CHCl_3$), -164.7°(365)(c=0.052, $CHCl_3$). Ms Calcd for $C_{18}H_{18}O_6$: M, 330.110. Found m/z: M^+, 330.109.

(+)- and (-)-Taxifolin 5,7,3',4'-Tetramethyl Ether (2f)

A solution of (±)-2f (40.0 mg) in methanol (0.2 ml) was chromatographed.

(+)-Enantiomer: Colorless needles of mp 158-160°C (EtOH). Rt 11.99 min. Yield, 18.3 mg (46%). Optical rotation $(\alpha)^{27}$(nm): +26.7°(589), +29.0°(577), +35.1°(546), +92.4°(435)(c=1.26, $CHCl_3$), +266.7°(365)(c=0.063, $CHCl_3$). Ms Calcd for $C_{19}H_{20}O_7$: M, 360.121. Found m/z: M^+, 360.121.

(-)-Enantiomer: Colorless fine needles of mp 155-157°C (EtOH). Rt 13.98 min. Yield, 19.4 mg (49%). Optical rotation $(\alpha)^{27}$(nm): -25.5°(589), -27.4°(577), -33.3°(546), -87.1°(435)(c=1.13, $CHCl_3$), -256.1°(365)(c=0.057, $CHCl_3$). Ms Calcd for $C_{19}H_{20}O_7$: M, 360.121. Found m/z: M^+, 360.122.

(+)- and (-)-Fustin 3-Acetyl-7,3',4'-trimethyl Ether (3b)

A solution of (±)-3b (20.5 mg) in methanol (0.1 ml) was chromatographed.

(+)-Enantiomer: Colorless needles of mp 120-122°C (EtOH). Rt 14.18 min. Yield, 9.2 mg (45%). Optical rotation $(\alpha)^{28}$(nm): +27.4°(589), +30.4°(577), +34.2°(546), +68.2°(435)(c=0.85, $CHCl_3$), +216.8°(365)(c=0.0425, $CHCl_3$). Ms Calcd for $C_{20}H_{20}O_7$: M, 372.121. Found m/z: M^+, 372.121.

(-)-Enantiomer: Colorless needles of mp 119-121°C (EtOH). Rt 16.83 min. Yield, 8.5 mg (41%). Optical rotation $(\alpha)^{28}$(nm): -26.1°(589), -28.4°(577), -30.6°(546), -72.8°(435)(c=0.85, $CHCl_3$), -240.2°(365)(c=0.0425, $CHCl_3$). Ms Calcd for $C_{20}H_{20}O_7$: M, 372.121. Found m/z: M^+, 372.121.

(+)- and (-)-Aromadendrin 3-Acetyl-5,7,4'-trimethyl Ether (3c)

A solution of (±)-3c (29.0 mg) in methanol (0.1 ml) was chromatographed.

(+)-Enantiomer: Colorless needles of mp 126-127°C (EtOH). Rt 16.91 min. Yield, 15.1 mg (52%). Optical rotation $(\alpha)^{24}$(nm): +35.1°(589), +37.8°(577),

+44.3°(546), +92.9°(435)(c=0.60, $CHCl_3$), +515.1°(365)(c=0.0325, $CHCl_3$). Ms Calcd for $C_{20}H_{20}O_7$: M, 372.121. Found m/z: M^+, 372.120.

(-)-Enantiomer: Colorless needles of mp 123.5-124°C (EtOH). Rt 20.43 min. Yield, 12.5 mg (43%). Optical rotation $[\alpha]^{24}$(nm): -34.1°(589), -37.0°(577), -42.9°(546), -84.9°(435)(c=0.61, $CHCl_3$), -541.9°(365)(c=0.031, $CHCl_3$). Ms Calcd for $C_{20}H_{20}O_7$: M, 372.121. Found m/z: M^+, 372.120.

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