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Structure determination and absolute configuration of cannabichromanone derivatives from high potency *Cannabis sativa*

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Abstract

Three new cannabichromanone derivatives were isolated from high potency cannabis, along with the known cannabichromanone. Full spectroscopic data, including the use of electronic circular dichroism and Mosher ester analysis to determine the absolute configuration of these compounds, are reported. All isolates were tested for antimicrobial, antimalarial, antileishmanial and anti-oxidant activity.

Keywords

Cannabis sativa; Absolute configuration; Cannabichromanone; Circular dichroism; Mosher ester analysis; Antimicrobial; Antimalarial; Antileishmanial; Anti-oxidant

Cannabis. sativa L. is one of the oldest medicinal plants known, having been used for more than five thousand years.[1] Cannabis has an extremely complex and diverse chemistry due to the vast number of its constituents and their possible interaction with one another.[2–3] Phytocannabinoids are unique to cannabis and are responsible for a wide range of biological activities including analgesic,[4] anti-emetic,[5] antidepressant,[6] appetite stimulation,[7] anticancer,[8] glaucoma treatment[9] and psychoactivity.[10]

As part of our phytochemical investigation[11–13] of high potency cannabis[14] (Δ^9-THC>10% by dry weight), we herein report the isolation of three new cannabichromanone derivatives (**2–4**) (Figure 1) and the known cannabichromanone (**1**), including the first report of the full

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spectroscopic data and absolute configuration for **1**. All compounds were evaluated for antimicrobial,[15] antimalarial,[16] antileishmanial[11,17] and anti-oxidant activity.[18]

Whole buds of mature female plants grown from high potency Mexican seeds were processed and stored at low temperature (−24°C). The material was authenticated by Dr. Suman Chandra, The University of Mississippi, and a voucher specimen (S1310V1) was deposited at the Coy Waller Complex, The University of Mississippi.

Plant material (9.0 kg, *ca*. 10% THC) was sequentially extracted at room temperature [hexanes (2 × 60 L), CH_2Cl_2 (48 L), EtOAc (40 L), EtOH (37.5 L), EtOH/H_2O (36 L, 1:1) and H_2O (40 L)] and the extracts concentrated under reduced pressure at 40°C. The hexanes extract (0.96 kg) was subjected to vacuum liquid chromatography (VLC) on flash silica gel eluting with hexanes, EtOAc and MeOH gradient. The hexanes/EtOAc (50:50) fraction was subjected to column chromatography and final purification by semi-preparative C18 HPLC (MeCN/H_2O, 75:25) afforded **1** (15 mg, R_t = 14 min), **2** (30 mg, R_t = 10 min), **3** (4 mg, R_t = 8 min) and **4** (60 mg, R_t = 8.5 min).

Compound **1** was obtained as a yellow oil {$[\alpha]^{25}_D$ -25.19 (*c* 0.5, $CHCl_3$)} and its molecular formula was determined to be $C_{20}H_{28}O_4$ by HRESIMS [*m/z* calcd for $C_{20}H_{28}O_4Na$: 355.1885 $(M+Na)^+$, found 355.1901], representing seven degrees of unsaturation. The IR spectrum exhibited hydroxyl and conjugated carbonyl absorption bands at 3346 and 1632 cm^{-1}, respectively. The ^{13}C-NMR, DEPT-135 and HMQC spectra of **1** revealed the presence of 20 carbon resonances, including four methyl, six methylene, three methine and seven quaternary carbons [two oxyaryl (C-1, C-4a), two carbonyl (C-8, C-3", IR absorption at 1632 and 1730 cm^{-1}, respectively), two aryl sp^2 (C-3, C-8a) and one oxygenated sp^3 (C-6) carbon]. The ^{1}H-NMR spectrum of **1** (Table 1) showed two aromatic protons at δ_H 6.18 (s, H-2) and 6.26 (s, H-4), four methyl signals at δ_H 0.86 (t, H-5'), 1.38 (s, H-9), 1.43 (s, H-10) and 2.12 (s, H-4"), six methylenes at δ_H 2.47 (t, H-1'), 1.56 (m, H-2'), 1.28 (m, H-3' and H-4'), 2.00 (m, H-1") and 2.59 (m, H-2"), one methine at δ_H 2.40 (dd, H-7) and a sharp singlet at δ_H 11.52 (Ar-O*H*). The downfield shift of this phenolic proton compared to the usual range of 5–8 ppm is due to hydrogen bonding with the C-8 carbonyl oxygen and was further confirmed by HMBC correlations with C-1, C-2 and C-8a (Figure 2). Detailed 2D NMR and UV (λ_{max} at 210, 279 and 350 nm)[19] experiments confirmed the presence of a 4-chromanone ring system with hydroxyl group at C-1, *n*-pentyl moiety at C-3, dimethyl at C-6 and 3"-oxobutyl moiety at C-7 (Figure 2), establishing **1** as cannabichromanone A[20] (Figure 1) [name based on 4-chromanone system: 5-hydroxy-2,2-dimethyl-3-(3-oxobutyl)-7-*n*-pentylchroman-4-one[21]].

Compound **2** was obtained as a yellow oil {$[\alpha]^{25}_D$ -19.81 (*c* 0.5, $CHCl_3$)} and its molecular formula was determined to be $C_{21}H_{30}O_5$ by HRESIMS [*m/z* calcd for $C_{21}H_{31}O_5$: 363.2171 $(M+H)^+$, found 363.2052], representing seven degrees of unsaturation. Compound **2** has the same basic structure as **1**, with the exception of an additional hydroxymethine functionality [δ_H 4.20 (m, H-1"), δ_C 73.2 (C-1")] established by COSY correlations (H-7/H-1", H-1"/H_2-2") and HMBC (H-1"/C-6, C-2", C-3" and C-8), confirming **2** as cannabichromanone B (Figure 1) [name based on 4-chromanone system: 5-hydroxy-3-(1-hydroxy-4-oxopentyl)-2,2-dimethyl-7-*n*-pentylchroman-4-one[21]].

Compound **3** was obtained as a yellow oil {$[\alpha]^{25}_D$ +7.99 (*c* 0.01, $CHCl_3$)} and its molecular formula was determined to be $C_{21}H_{28}O_5$ by HRESIMS [*m/z* calcd for $C_{21}H_{28}O_5Na$: 383.1834 $(M+Na)^+$, found 383.1838], representing eight degrees of unsaturation. Compound **3** has the same basic structure as **1** and **2**, except for an additional carbonyl moiety [δ_C 207.7 (C-4")] established by HMBC (H_2-1"/C-3", H_3-5"/C-3", C-4"), confirming **3** as cannabichromanone C (Figure 1) [name based on 4-chromanone system: 5-hydroxy-2,2-dimethyl-3-(3,4-dioxopentyl)-7-*n*-pentylchroman-4-one[21]].

Compound **4** was obtained as a yellow oil {$[\alpha]^{25}_{D}$ -14.13 (*c* 0.5, $CHCl_3$)} and its molecular formula was determined to be $C_{21}H_{28}O_3$ by HRESIMS [*m/z* calcd for $C_{21}H_{27}O_3$: 329. 2117 $(M+H)^+$, found 329.2089], representing eight degrees of unsaturation. The ^{13}C-NMR spectrum showed signals indicating four methyl, six methylene, four methine and seven quaternary carbons [two oxyaryl (C-1, C-4a), one carbonyl (C-8, IR absorption at 1730 cm^{-1}), two aryl sp^2 (C-3, C-8a), one oxygenated sp^2 (C-4") and one oxygenated sp^3 (C-6) carbon]. The ^{1}H-NMR spectrum of **4** (Table 1) showed two aromatic protons at δ_H 6.52 (s, H-2) and 6.34 (s, H-4), one olefinc proton at δ_H 5.91 (br s, H-3"), four methyl signals at δ_H 0.84 (t, H-5'), 1.15 (s, H-9), 1.41 (s, H-10) and 1.94 (s, H-5"), six methylenes at δ_H 2.42 (t, H-1'), 1.52 (m, H-2'), 1.27 (m, H-3', H-4'), 1.38 (m, H-1") and 2.36 (m, H-2"), and one methine at δ_H 2.65 (dd, H-7). HMBC and COSY experiments (Figure 2) confirmed the presence of a substituted 4-chromanone system with UV absorption maxima λ_{max} 209, 279 and 350 nm. The absence of a chelated hydroxyl proton at *ca.* δ_H 11.5, the upfield shift of C-1 to δ_C 144.8, the molecular formula, degrees of unsaturation and 2D NMR analysis (Figure 2) pointed towards an oxygen-bridge between C-4" and C-1, resulting in a rare nine membered ring.[22–23] The geometry of the $\Delta^{3",4"}$ system was assigned as *Z* on the basis of ROESY correlations between H-3" and H_3-5", establishing **4** as cannabichromanone D (Figure 1) [name based on 4-chromanone system: 2,2-dimethyl-3,5-(4-yloxypent-3-en-1-yl)-7-*n*-pentylchroman-4-one[21]].

Conformational analysis of **3** indicated the sofa conformation (E-conformer), with the pentane-3",4"-dione group at C-7 in the pseudoequatorial position and the two methyls at C-6 in the equatorial and axial positions, as the lowest energy conformer (Figure 3). This was confirmed by ROESY analysis indicating correlation between H_{ax}-7 [δ_H 3.12 (d)] and H_3-10 [δ_H 1.46 (s), δ_C 26.0 (equatorial)], while no correlation was observed between H_{ax}-7 [δ_H 3.12 (d)] and H_3-9 [δ_H 1.38 (s), δ_C 23.3 (axial)]. Correlation between H_{ax}-7 and both H_3-9 and H_3-10 would suggest an unfavorable C-6/C-7 *trans*-diaxial configuration.

Optical rotatory dispersion (ORD) and electronic circular dichroism (CD) have been used to determine the absolute configuration and conformation of natural products, e.g. flavonoids,[24] and in qualitative analysis of THC and CBD content.[25] The modified octant rule,[26] defining the relationship between the chirality of α,β-unsaturated ketones and the sign of their high wavelength Cotton effect (CE), was extended to aryl ketones or acetophenones.[27] Compound **3** shows UV absorption at 279 nm ($\pi\rightarrow\pi^*$) and 350 nm ($n\rightarrow\pi^*$) and applying the octant rule modified for cyclic arylketones, a positive CE for the $n\rightarrow\pi^*$ carbonyl transition would indicate 7*R* and a negative CE for the $n\rightarrow\pi^*$ carbonyl transition would indicate 7*S* absolute configuration.[24] A positive CE at 313 nm (0.2 mg/ml, MeOH) was observed for **3** (Figure 4), establishing the absolute configuration as 7*R*. Conversely, **1**, **2** and **4** displayed negative CE at the $n\rightarrow\pi^*$ carbonyl transition (320–350 nm), indicting 7*S* absolute configuration for these compounds (Table 2).

The absolute configuration of **2** at the secondary carbinol chiral center (C-1") was determined via the Mosher ester analysis protocol.[28–31] This protocol involves derivatization of the carbinol with each of the enantiomeric pair (*R*)-(−)-MTPA-Cl and (*S*)-(+)-MTPA-Cl (α-methoxy-α-trifluoromethylphenylacetyl chloride) giving two diastereoisomeric esters [(*S*)- and (*R*)-ester, respectively]. NMR analysis of each of the two esters can be used to determine the absolute configuration of the chiral center. The NMR analysis is based on an empirical conformation for the esters that dictate the spectroscopic features of the conformers. This conformation includes an *s-trans* (antiperiplanar) arrangement about the O-CO bond and a *syn*-coplanar (0° dihedral angle) arrangement between of the CF_3 group and the carbinol methine proton with respect to the carbonyl group (Figure 5). The MTPA aryl substituent causes an anisotropic, magnetic shielding effect on protons above or below the plane of the aryl ring, resulting in an upfield chemical shift for the spatially proximal protons in the NMR spectrum. This implies that protons in the R^2-group of the (*S*)-ester are more shielded and hence

upfield. The same applies for protons in the R^1-group of the (*R*)-ester. The sign of $\Delta\delta_H(SR) = \delta_H(S) - \delta_H(R)$ for protons in R^1 will therefore be positive and for protons in R^2 negative, yielding the absolute configuration of the secondary carbinol chiral center. The (*S*)- and (*R*)-MRPA-esters for **2** were prepared as follows: In a NMR tube **2** (2 mg) in pyridine-d_5 (100 μl) was reacted with (*R*)-(−)-MTPA-Cl (30 μl) at room temperature (2 hours) to afford (**2*S***)-ester. Similarly, (**2*R***)-ester was prepared from (*S*)-(+)-MTPA-Cl. ^{1}H-NMR data was measured directly from the reaction mixtures (Table 3). A negative $\Delta\delta_H(SR)$ for H-7 indicates aryl-shielding of the C-7 moiety in the (*S*)-ester and therefore 1"*R* absolute configuration, establishing **2** as 5-hydroxy-3*S*-(1*R*-hydroxy-4-oxopentyl)-2,2-dimethyl-7-*n*-pentylchroman-4-one.

The isolated compounds were evaluated for antimicrobial (*Candida albicans* ATCC 90028, *Escherichia coli* ATCC 35218, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium intracellulare* ATCC 23068, *Aspergillus fumigat* ATCC 90906 and Methicillin Resistant *Staphylococcus aureus* ATCC 43300), antimalarial [*Plasmodium falciparum* (chloroquine sensitive D6 clone) and *P. falciparum* (chloroquine resistant W2 clone)], antileishmanial and anti-oxidant activity.

The isolated compounds showed no antimicrobial activity. Compounds **1** and **3** showed mild antimalarial activity against *P. falciparum* (D6 and W2 clone) with IC_{50} values of 3.7 and 3.8 μg/mL, and 4.7 and 3.4 μg/mL, respectively. Compounds **2** and **4** displayed no antimalarial activity. Compounds **1–4** showed moderate antileishmanial activity with IC_{50} values of 14.0, 14.0, 12.5 and 9.0 μg/mL, respectively.

A TLC autographic assay for 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical-scavenging effect was used to determine anti-oxidant activity. The isolated compounds were dissolved in DMF (2 mg/mL) and applied in the form of a spot (4 μl, 4–5 mm in diameter) on silica gel GF plates. The residual DMF was removed under vacuum (15–20 min). A similar amount of vitamin E in DMF was used as positive anti-oxidant control. The radical-scavenging effects of the compounds were detected on the TLC plate using DPPH spray reagent (0.2% w/v in methanol). The plate was observed 30 min after spraying. Active compounds are observed as yellow spots against a purple background. Relative radical-scavenging activity was assigned as “strong” (compounds that produce an intense bright yellow spot), “medium” (compounds that produce a clear yellow spot), “weak” (compounds that produce a weakly visible yellow spot), or “not active” (compounds that produce no yellow spot).[32] Vitamin E produced an intense bright yellow spot. The isolated compounds all produced a bright yellow spot, indicating “strong” anti-oxidant activity.

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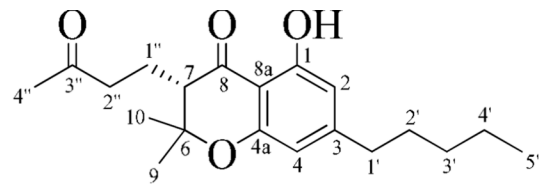

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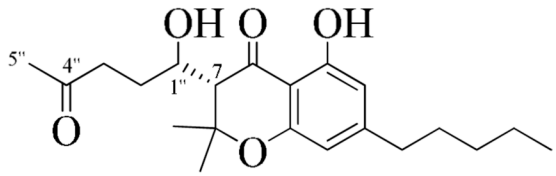

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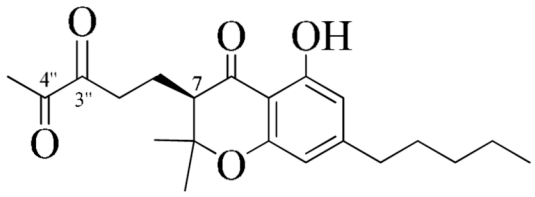

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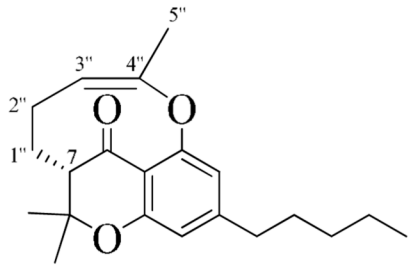

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Figure 1.
Cannabichromanone derivatives **1–4** with cannabinoid numbering system.[21]

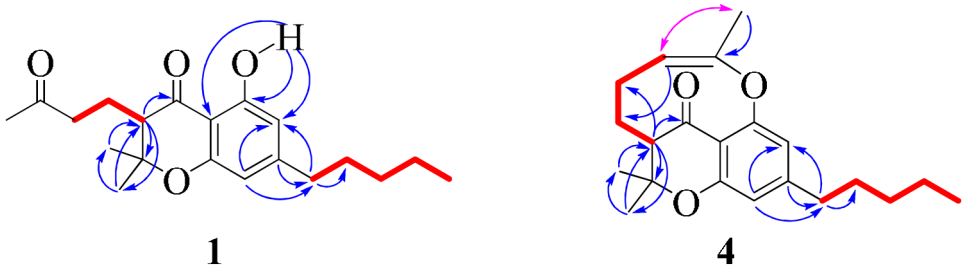


Figure 2.
Important HMBC (blue arrows), COSY (red bold) and ROESY (purple double-faced arrow) correlations of **1** and **4**.

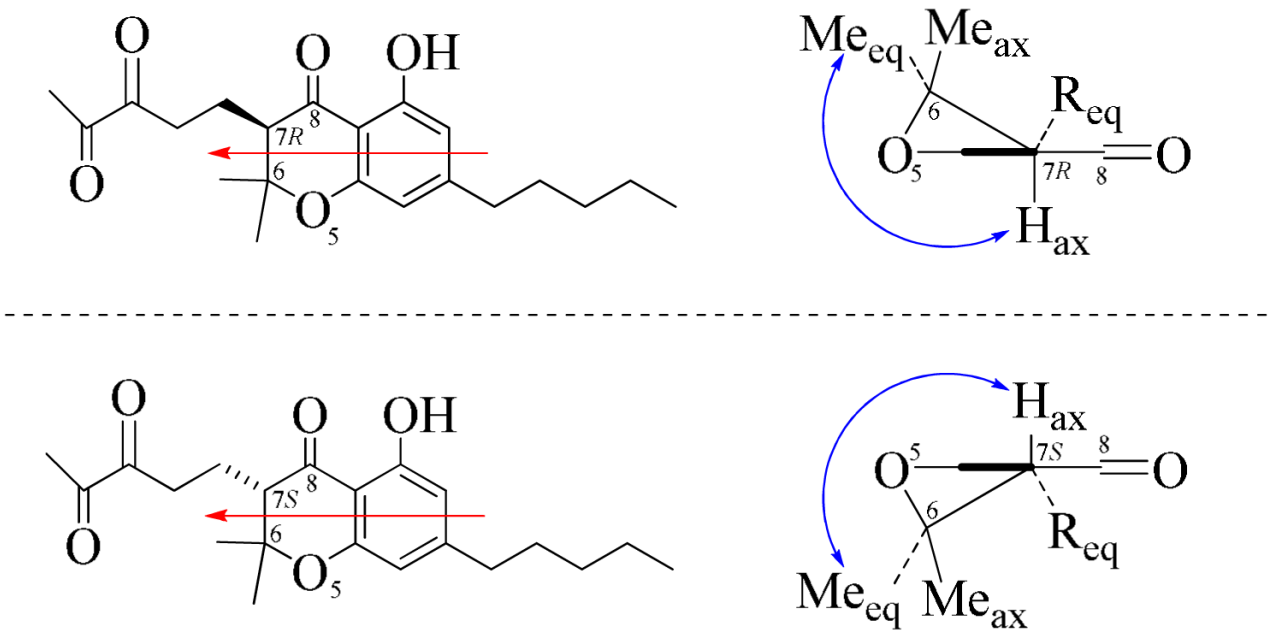


Figure 3.

Conformational analysis for **3**. The red arrow indicates the direction of projection. The back wedge represents the plane of the benzenoid ring. The blue arrow indicates ROESY correlation between H_3-9 or H_3-10 and H-7.

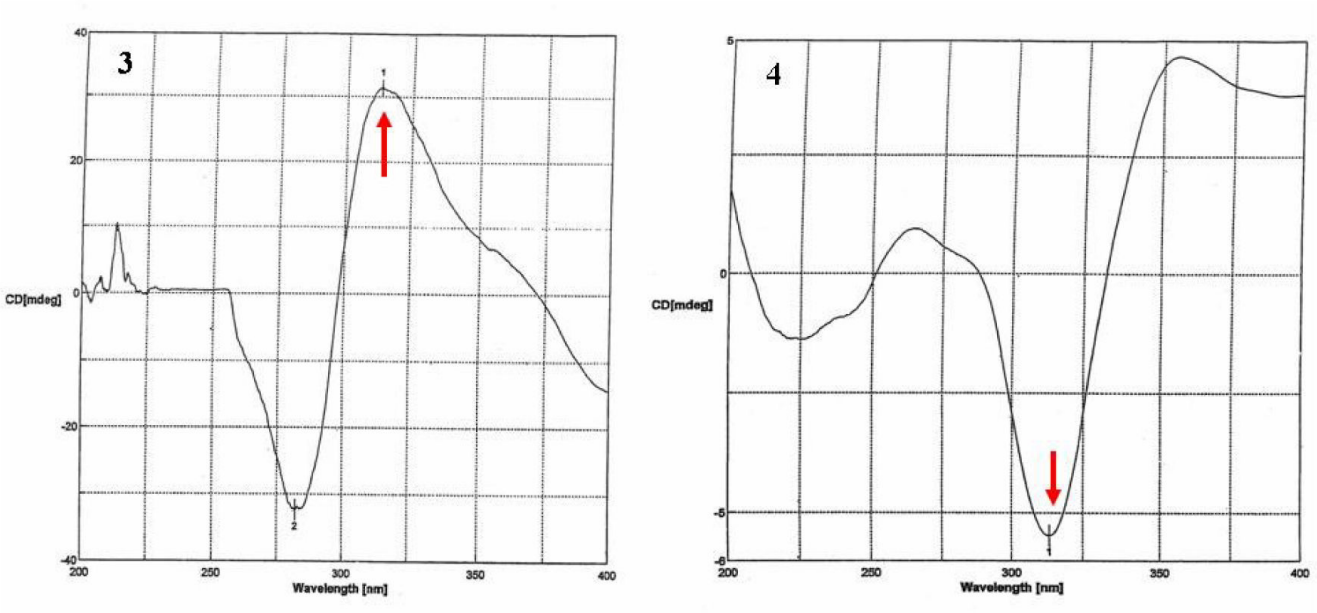
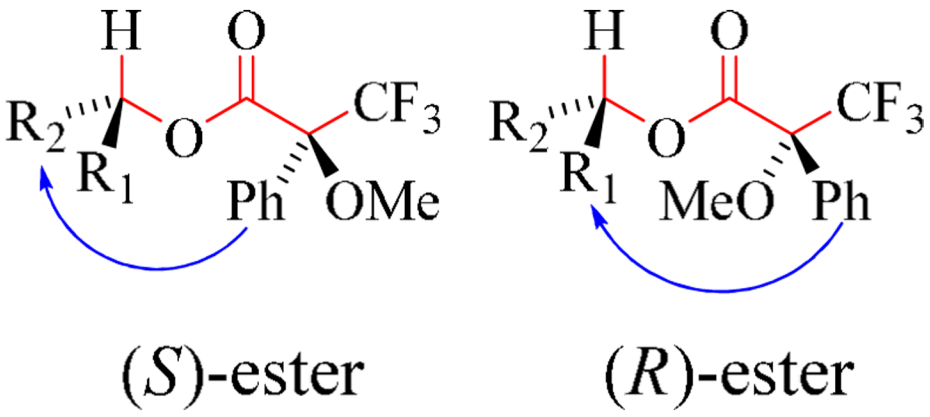


Figure 4.
CD spectra for **3** and **4**.



(*S*)-ester (*R*)-ester

Figure 5.
Conformation of (*S*)- and (*R*)-esters. The atoms and bonds in red are coplanar. The blue arrow indicates the phenyl shielding effect

Table 1

^{1}H- and ^{13}C-NMR data of **1–4** in $CDCl_3$ (500 MHz for ^{1}H, 100 MHz for ^{13}C)[a]

No	1		2		3		4	
	δ_C	δ_H (mult, *J*)	δ_C	δ_H (mult, *J*)	δ_C	δ_H (mult, *J*)	δ_C	δ_H (mult, *J*)
1	161.8		161.8		163.9		144.8	
2	107.9	6.18 (s)	108.0	6.17 (s)	114.4	6.66 (s)	111.4	6.52 (s)
3	155.5		155.7		156.3		133.1	
4	108.7	6.26 (s)	108.8	6.25 (s)	117.0	6.42 (s)	116.2	6.34 (s)
4a	159.3		159.3		156.3		140.7	
6	81.5		81.4		82.6		82.6	
7	53.6	2.40 (dd, 10.8)	53.4	2.40 (d, 6.4)	55.9	3.12 (d, 10.4)	54.5	2.65 (dd, 4.0, 14.0)
8	201.1		200.9		198.8		202.0	
8a	105.0		105.0		112.6		137.6	
9	23.4	1.38 (s)	23.6	1.36 (s)	23.3	1.38 (s)	20.7	1.15 (s)
10	26.6	1.43 (s)	26.4	1.41 (s)	26.0	1.46 (s)	26.8	1.41 (s)
1'	36.9	2.47 (t, 7.2)	36.9	2.47 (t, 7.2)	36.7	2.58 (t,7.2)	35.7	2.42 (t,7.2)
2'	30.3	1.56 (m)	30.2	1.56 (m)	30.3	1.60 (m)	31.5	1.52 (m)
3'	31.6	1.28 (m)	31.6	1.28 (m)	31.5	1.32 (m)	31.6	1.27 (m)
4'	22.7	1.28 (m)	22.7	1.28 (m)	22.7	1.32 (m)	22.8	1.27 (m)
5'	14.2	0.86 (t, 6.4)	14.2	0.84 (t, 6.4)	14.2	0.89 (t, 6.8)	14.3	0.84 (t, 6.4)
1"	20.3	2.00 (m)	73.2	4.20 (m)	19.9	2.18 (m)	25.4	1.38 (m)
2"	41.4	2.59 (m)	20.1	1.32 (m)	41.4	2.14, 2.46 (m)	31.9	2.36 (m)
3"	208.3		35.5	2.59 (m)	195.3		128.1	5.91 (br s)
4"	30.4	2.12 (s)	208.0		207.7		163.5	
5"			31.1	2.12 (s)	30.3	2.10 (s)	24.1	1.94 (s)
OH		11.52 (s)		11.46 (s)		11.11 (s)		

[a]Chemical shifts (δ) are in ppm. Coupling constants (*J*) are in Hz.

Table 2

Spectroscopic data for **1–4**

Compound	$[\alpha]^{25}_{D}$	CE at n→π* carbonyl transition	^{1}H-NMR for H-7	Absolute configuration at C-7
1	−	−	2.40	*S*
2	−	−	2.40	*S*
3	+	+	3.12	*R*
4	−	−	2.65	*S*

Table 3

Mosher ester analysis for 2

No	2 δ_H ($CDCl_3$)	2 δ_H (py-d_5)	(2*S*)-ester δ_H (py-d_5)	(2*R*)-ester δ_H (py-d_5)	$\Delta\delta_H$(*SR*)
7	2.40	2.67	2.64	2.57	+0.07
1"	4.20	4.53	5.61	5.65	−0.04
2"	1.32	1.21	1.23	1.25	−0.02
9_{ax}	1.36	1.33	1.31	1.32	−0.01
10_{eq}	1.41	1.44	1.40	1.39	+0.01

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