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TETRAHEDRON: *ASYMMETRY*

Synthesis and analytical properties of (*S*)-(+)-2-methoxy-2-(9-phenanthryl)propionic acid

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Abstract—2-Methoxy-2-(9-phenanthryl)propionic acid was synthesized as a novel chiral resolving agent. The absolute configuration of (+)-2-methoxy-2-(9-phenanthryl)propionic acid was determined to be *S* by using X-ray structural analysis of the (1*R*,2*S*,5*R*)-menthyl ester. In the crystal, the methoxyl and carbonyl groups of the ester are in a *syn*-periplanar position. The *syn*-periplanar conformations of (1*R*,2*S*,5*R*)-menthyl esters were also observed by the NMR analyses in $CDCl_3$. The utility of (*S*)-(+)-2-methoxy-2-(9-phenanthryl)propionic acid was exemplified by the resolution of (±)-3-octanol.

Mosher's 2-methoxy-2-(trifluoromethyl)phenylacetic acid (MTPA acid) **1** is widely used to determine the absolute configurations of secondary alcohols[1,2] (Fig. 1). We have been studying the use of 2-methoxy-2-(1-naphthyl)propionic acid (MαNP acid) **2**[3–7] for the stereochemical studies of biologically active natural products. Acid **2** is a non-racemizable chiral acid that is useful for preparing pure enantiomers[3–7] and for determining the absolute configuration of each enantiomer.[4] Herein we report the synthesis and absolute configuration of 2-methoxy-2-(9-phenanthryl)propionic acid **3**, which possesses a large aryl substituent 9-phenanthryl group (Fig. 1). The spectral and separation properties of acid **3** were corroborated using (1*R*,2*S*,5*R*)-menthyl esters. Finally, acid **3** was applied to the enantioresolution of (±)-3-octanol.

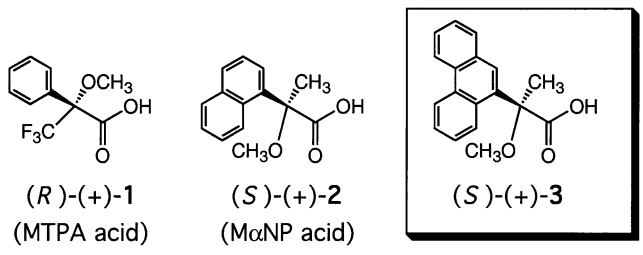

Figure 1. The structures of chiral resolving agents.

(±)-Methyl 2-hydroxy-2-(9-phenanthryl)propionate (±)-**4** was synthesized by the Grignard reaction of 9-phenanthrylmagnesium bromide and methyl pyruvate in THF (Scheme 1). The hydroxyl group of (±)-**4** was methylated with NaH and CH_3I in THF to give (±)-methyl 2-methoxy-2-(9-phenanthryl)propionate (±)-**5**. Alkaline hydrolysis ($NaOCH_3$/methanol) of (±)-**5** gave (±)-2-methoxy-2-(9-phenanthryl)propionic acid (±)-**3**. The racemic acid (±)-**3** was then condensed with (1*R*,2*S*,5*R*)-(−)-menthol using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in CH_2Cl_2. The crude product was purified by preparative LC (silica gel, hexane/EtOAc 19:1) to give (+)-**6a** {$[\alpha]_D^{30}$ +2.7 (*c* 1.45, chloroform)} as the first-eluted ester and (−)-**6b** {$[\alpha]_D^{31}$ −46 (*c* 1.21, ethanol)} as the second-eluted in 43 and 37% yield, respectively. Alkaline hydrolysis (KOH/aq. ethanol) of ester (+)-**6a** gave enantio-pure (+)-**3** {$[\alpha]_D^{30}$ +101 (*c* 0.982, ethanol)}. Therefore, (+)-**6a** and (−)-**6b** are (1*R*,2*S*,5*R*)-menthyl esters of (+)- and (−)-**3**, respectively. Acid (+)-**3** was methylated with trimethylsilyldiazomethane affording methyl ester (+)-**5** {$[\alpha]_D^{29}$ +86 (*c* 0.97, ethanol)}. Acid (−)-**3** {$[\alpha]_D^{28}$ −100 (*c* 0.914, ethanol)}, and methyl ester (−)-**5** {$[\alpha]_D^{28}$ −86 (*c* 0.90, ethanol)} were also prepared from ester (−)-**6b**.

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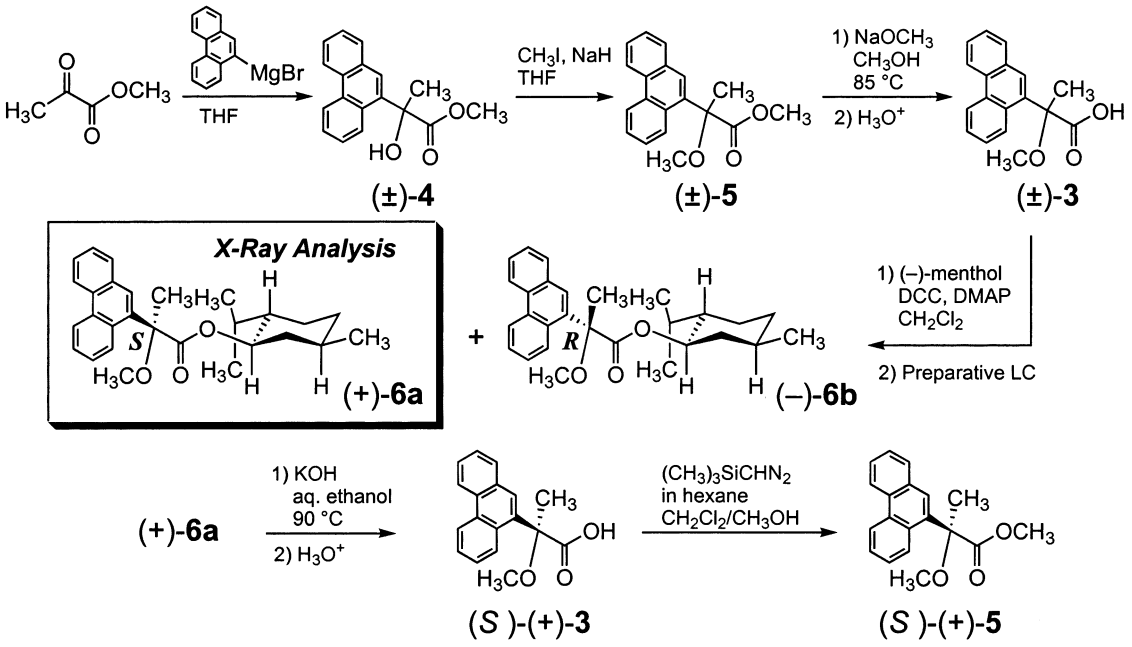

Scheme 1. Synthesis and resolution of 2-methoxy-2-(9-phenanthryl)propionic acid **3**.

The ^{1}H NMR signals of esters (+)-**6a** and (–)-**6b** (600 and 800 MHz, $CDCl_3$) were assigned from DQF COSY, HSQC, and HMBC spectra (Fig. 2). The $\Delta\delta$ ($=\delta$((–)-**6b**)$-\delta$((+)-**6a**)) values are shown in Figure 2. The chemical shifts of esters (+)-**6a** and (–)-**6b**, and their $\Delta\delta$ values are close to those of the (*S*)- and (*R*)-MαNP esters of (1*R*,2*S*,5*R*)-(–)-menthol,[5,6] in spite of the difference between the 9-phenanthryl and 1-naphthyl groups. High field shifts were observed at the 6-β proton of ester (+)-**6a** (0.48 ppm), and at the isopropyl group of ester (–)-**6b** (0.15, 0.18, 0.49 ppm). Negative $\Delta\delta$ values were observed at 2- and 3-positions, and the isopropyl group. Conversely, positive $\Delta\delta$ values were observed at 5- and 6-positions (Fig. 2). The ^{1}H NMR spectra also revealed that esters (+)-**6a** and (–)-**6b** are both >99.8% d.e.

Recently, Kitamura et al. discussed inter- and intramolecular OH···O=C hydrogen bonds and the limits of empirical NMR studies for determining the relative stereochemistry of aldols.[8] They noted that X-ray diffraction is the only reliable spectroscopic method.[8] Although the MαNP esters of (1*R*,2*S*,5*R*)-(–)-menthol are not crystalline, ester (+)-**6a** is readily crystallized from ethyl acetate. Consequently, the relative stereochemistry of ester (+)-**6a** was determined by X-ray structural analysis (Fig. 3 and Table 1). The absolute configuration of the acyl group was assigned as *S*, because (1*R*,2*S*,5*R*)-(–)-menthol was used for ester (+)-**6a**. Therefore, the absolute stereochemistry of acid (+)-**3** was determined to be *S*. The crystalline structure of ester (+)-**6a** shows that hydrogen atom H22 and the carbonyl group of ester (+)-**6a** are in a *syn*-periplanar position: the dihedral angles ϕ(H22–C22–O1–C19)$=$ 6.6°; ϕ(C22–O1–C19–O2)$=-6.8°$. The two oxygen atoms of the methoxyl and carbonyl groups are also in a *syn*-periplanar position: the dihedral angle ϕ(O2–C19–C18–O3)$=11.8°$. The crystalline structure of ester (+)-**6a** suggests that 5- and 6-positions of (1*R*,2*S*,5*R*)-menthyl group are located above aromatic

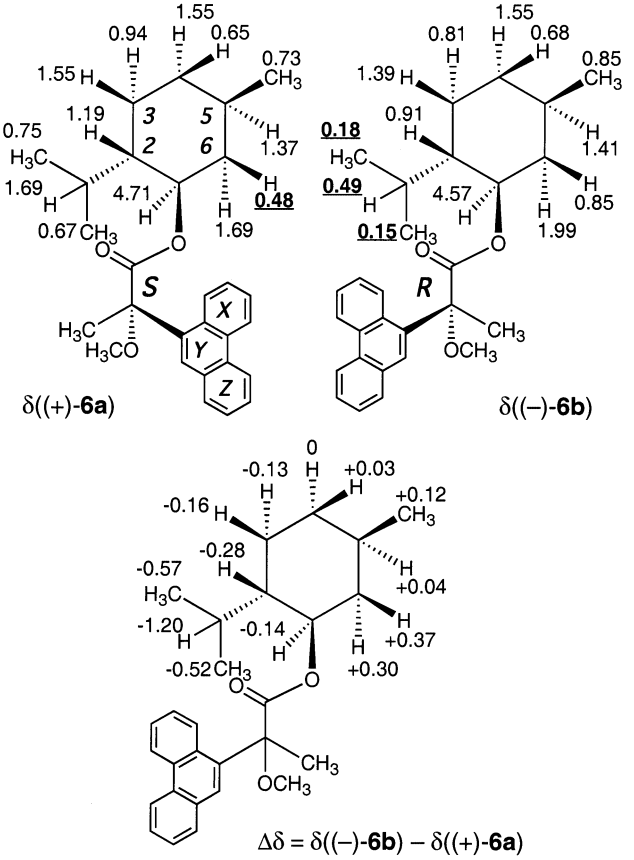

Figure 2. The ^{1}H NMR chemical shift data and $\Delta\delta$ values for (+)-**6a** and (–)-**6b** (800 MHz, $CDCl_3$).

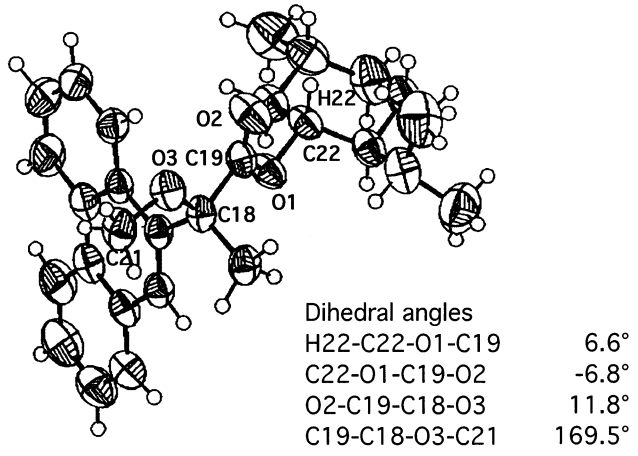

Figure 3. The stereochemistry of ester (+)-**6a** determined by X-ray crystallography.

Table 1. Crystallographic data for (+)-**6a**

Mol. formula	$C_{28}H_{34}O_3$
Crystal system	Monoclinic
Space group	$P2_1$
Z	2
a (Å)	12.253(4)
b (Å)	9.973(4)
c (Å)	10.082(3)
V (Å^3)	1214.1(7)
β (°)	99.74(3)
ρ_{calcd}	1.145
R	4.27
R_w	4.58

rings X and Y (Fig. 3). These conformational features in the crystal are consistent with those determined from the ^{1}H NMR analyses of ester (+)-**6a** in $CDCl_3$ (Fig. 2). We have already reported the *syn*-periplanar conformation of MαNP esters in $CDCl_3$.[3–7]

The preferred conformation of *O*-methylmandelic acid esters has been studied by Trost et al.,[9] who reported that in the *O*-methylmandelates, the methoxyl group eclipses the ester carbonyl group. The esters of acid **3** have the structure and conformation similar to those of *O*-methylmandelates as shown in Figure 4: (1) the methyl group replaces the α hydrogen atom of *O*-methylmandelate to prevent epimerization; (2) the 9-phenanthryl group replaces the phenyl group to enhance the ^{1}H NMR anisotropy effect.

Conformer **L**, which was observed in the crystal, explained the ^{1}H NMR high field shifts observed at 5- and 6-positions of the (1*R*,2*S*,5*R*)-menthyl group of ester (+)-**6a** (Fig. 5). The repulsion between the 3′ methyl group and hydrogen atom Ha at the 10-position of the 9-phenanthryl group is not crucial in conformer **L**. By contrast, conformer **M** is not plausible because of the repulsion between the 3′ methyl group and hydrogen atom Hb at the 8-position (Fig. 5).

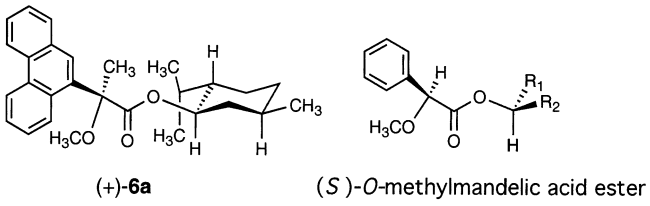

Figure 4. The preferred conformation of (+)-**6a** and (*S*)-*O*-methylmandelic acid ester.

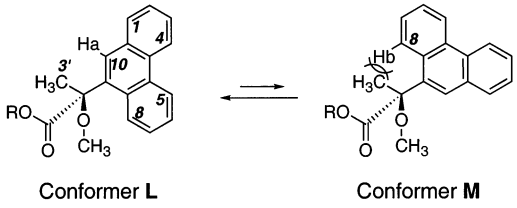

Figure 5. The orientation of the 9-phenanthryl group in ester (+)-**6a**.

Esters (+)-**6a** and (−)-**6b** were remixed, and analyzed by HPLC (Fig. 6). The separation factor (α value) was 1.64 in a SILICA SG80 column (4.6 ϕ×250 mm, hexane/EtOAc, T_0: solvent peak), and 1.16 in a CAPCELL-PAK C18 MG column (4.6 ϕ×150 mm, methanol/water 97:3, T_0: uracil). These separation factors ($\alpha = 1.64$ and 1.16) are equivalent to those for the enantioresolution of *rac*-menthol using single-enantiomer **3**.

Finally, the utility of acid (*S*)-(+)-**3** was exemplified by the enantioresolution of (±)-3-octanol, both enantiomers of which are known as the ant pheromones.[10] Acid (*S*)-(+)-**3** was condensed with (±)-3-octanol using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSCI·HCl) and DMAP in CH_2Cl_2. The crude product of diastereomeric esters was separated by preparative LC (silica gel, hexane/EtOAc 47:3) to give (+)-**7a** {38%, $[\alpha]_D^{31}$ +21 (*c* 0.44, ethanol)} and (+)-**7b** {40%, $[\alpha]_D^{32}$ +59 (*c* 0.42, ethanol)}: the separation factor $\alpha = 1.57$ with the SILICA SG80 column (Fig. 7). The ^{1}H NMR chemical shift data of (+)-**7a** and (+)-**7b** are shown in Figure 8 together with the $\Delta\delta$ values, from which the absolute configuration of the first-eluted fraction (+)-**7a** was unambiguously determined as $X = R$. (See Ref. 4 for the definition of $\Delta\delta$ and the sector rule for the assignment of absolute configuration.) Therefore, the absolute configurations of these esters are described as (*S*,*R*)-(+)-**7a** and (*S*,*S*)-(+)-**7b**, respectively. The ester (*S*,*S*)-(+)-**7b** was treated with $NaOCH_3$/methanol to yield enantiopure (*S*)-(+)-3-octanol {81%, $[\alpha]_D^{31}$ +9.7 (*c* 0.11, chloroform)}; this assignment of the absolute configuration is consistent with the previous one {Ref. 10, (*S*)-(+)-3-octanol: $[\alpha]_D^{22}$ +10.1 (*c* 0.82, chloroform)}. Namely, the enantioresolution of alcohols using acid (*S*)-(+)-**3** and the following determination of absolute configuration by the ^{1}H NMR anisotropy method are thus powerful.

As discussed above, 2-methoxy-2-(9-phenanthryl)-propionic acid **3** was synthesized as a novel chiral resolving agent. The absolute configuration of (+)-**3** was

determined to be *S* via X-ray structural analysis of ester (+)-**6a**. The large aryl substituent 9-phenanthryl group contributed to the formation of the crystal. The crystalline structure of (+)-**6a** revealed that the two oxygen atoms of the carbonyl and methoxyl groups are in the *syn*-periplanar position. A similar conformation has been proposed for MαNP esters, although the mechanism is not clear.[4,11] The *syn*-periplanar conformations of the methoxyl and carbonyl groups were also supported by the NMR analyses of esters (+)-**6a** and (−)-**6b** in $CDCl_3$. Acid (*S*)-(+)-**3** was used in the enantioresolution of (±)-3-octanol. The novel chiral carboxylic acid (*S*)-(+)-**3** could be used to prepare single-enantiomer agrochemicals[12] and pharmaceuticals, and for stereochemical studies of natural products along with other chiral resolving agents.

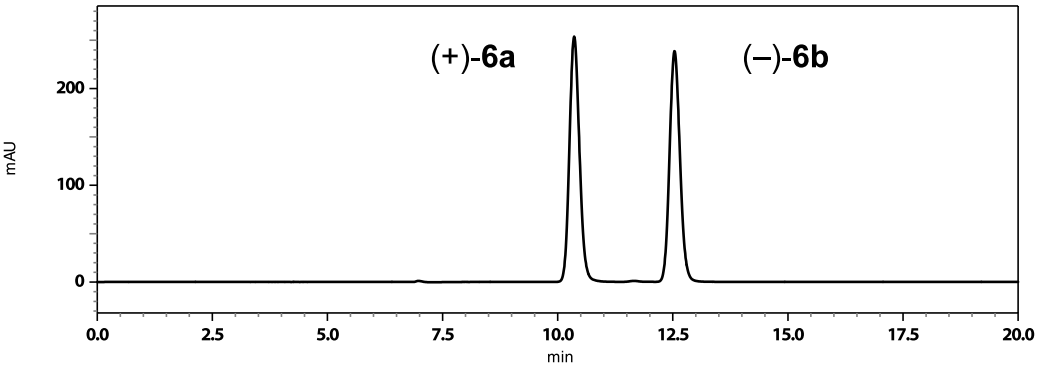

Figure 6. The HPLC separation of diastereomeric esters (+)-**6a** and (−)-**6b** (SILICA SG80, hexane/EtOAc 9:1, UV 300 nm, $\alpha = 1.64$).

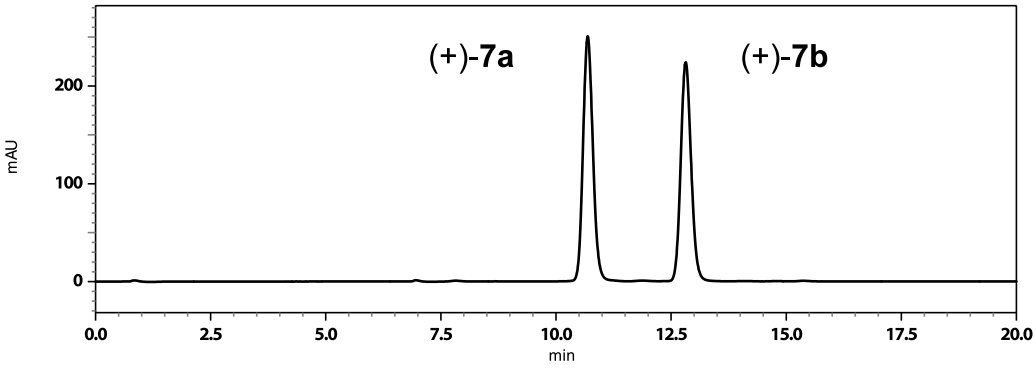

Figure 7. The HPLC separation of diastereomeric esters formed from (±)-3-octanol and (*S*)-(+)-**3** (SILICA SG80, hexane/EtOAc 9:1, UV 300 nm, $\alpha = 1.57$).

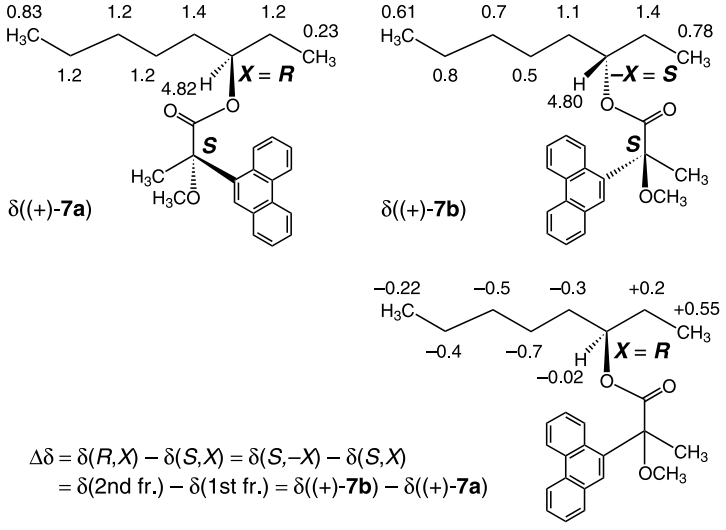

Figure 8. The ^1H NMR chemical shift data and $\Delta\delta$ values for esters (+)-**7a** and (+)-**7b** (600 MHz, $CDCl_3$).

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