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Unambiguous Determination of the Absolute Configurations of Acetylene Alcohols by Combination of the *Sonogashira* Reaction and the CD Exciton Chirality Method – Exciton Coupling between Phenylacetylene and Benzoate Chromophores

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Summary. The CD exciton chirality method was applied to various phenylacetylene alcohols to determine their absolute configurations; the long axis polarized π–π^* transition ($\lambda_{max} = 252$ nm) of the 4-methoxyphenylacetylene chromophore couples with the transition ($\lambda_{max} = 257$ nm) of the 4-methoxybenzoate group to generate intense exciton split CD *Cotton* effects, from the signs of which the absolute configurations of phenylacetylene alcohols were unambiguously determined. As an extension of the results, a new methodology for determining the absolute configurations of acetylene alcohols having the HC≡CCH(OH)-moiety by combination of the *Sonogashira* reaction and the CD exciton chirality method has been developed and applied. Since the π–π^* transition of acetylene triple bond is located below 180 nm, it is difficult to observe ideal bisignate CD *Cotton* effects due to the exciton coupling between acetylene and benzoate chromophores. To observe the ideal exciton split *Cotton* effects necessary for the unambiguous determination of absolute configuration, the terminal acetylene group was converted, by the *Sonogashira* reaction, to the 4-methoxyphenylacetylene moiety, which exhibits an intense π–π^* absorption band polarized along the long axis of the chromophore at 252 nm. As a partner of exciton coupling, 4-methoxybenzoate showing a π–π^* band at 257 nm was introduced into the alcohol moiety, and the benzoates formed showed intense bisignate CD *Cotton* effects, from the signs of which the absolute configurations of original acetylene alcohols could be determined in an unambiguous manner.

Keywords. Exciton CD; Absolute configuration; CD exciton chirality method; Chiral phenylacetylene alcohol; *Sonogashira* reaction.

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Introduction

It is well known that the molecular chirality is essential to life processes, and most biologically active compounds controlling physiological functions of living organisms are chiral. Hence in the structural study of biologically active compounds, including natural products, the determination of absolute configuration becomes the first major issue. The methodologies for determining the absolute configurations of chiral compounds are classified into the following two categories: a) nonempirical methods; there are the *Bijvoet* method of X-ray crystallography [1] and the circular dichroism (CD) exciton chirality method [2]. These methods provide nonempirical determination of a target molecule's configuration without knowledge of the absolute configuration of reference compounds. In X-ray crystallography, since the anomalous dispersion effect of heavy atoms can be measured very accurately under proper conditions, the absolute stereostructure obtained is unambiguous and reliable. However, the X-ray method needs single crystals of suitable size for X-ray diffraction, and so the critical problem is how to obtain such single crystals. The CD exciton chirality method [2–4] is also useful because the absolute configuration can be determined in a nonempirical manner, and it does not require crystallization. Furthermore, even the absolute configurations of unstable compounds can be obtained by this method.

Another category is: b) relative and/or empirical methods for determining absolute configuration using an internal reference with known absolute configuration. Absolute configuration can be obtained by determining the relative configuration at the position of interest against a reference compound or substituent with known absolute configuration. A typical example is the X-ray crystallography taken after the introduction of a chiral auxiliary with known absolute configuration [5–7]. In this case, the absolute configuration of the point in question can be automatically determined using the chirality of the auxiliary introduced as an internal reference. The relative X-ray methods are expected to find widespread application.

Recently, the proton nuclear magnetic resonance (^{1}H NMR) anisotropy method has often been employed as a relative and empirical method [8–14]. In particular, the absolute configurations of secondary alcohols are frequently determined using the advanced *Mosher* method developed by *Kusumi et al*. In this case, the absolute configurations of chiral auxiliaries, such as *Mosher*'s reagent [α-methoxy-α-(trifluoromethyl)phenylacetic acid (*MTPA*)] [8–10], *Trost*'s reagent [α-methoxyphenylacetic acid (*MPA*)] [11], and *Harada*'s reagent [2-methoxy-2-(1-naphthyl)propionic acid (*MαNP* acid)] [13, 14], are known, and the preferred conformation of the esters formed with chiral secondary alcohols and these chiral acids is rationalized. In addition, the aromatic substituent (phenyl or naphthyl group) generates a magnetic anisotropy effect due to the ring current induced under the external magnetic field, and so the proton NMR signals of the alcohol moiety facing the phenyl or naphthyl group in the preferred conformation are moved to a higher magnetic field (high field shift). By observing the ^{1}H NMR anisotropy effect, the absolute configuration of the alcohol part can be determined in an empirical manner.

These nonempirical and empirical methods are based on totally different physical phenomena, but when those methods are applied to a specific compound, they should give the same conclusion of absolute configuration, of course. In this paper,

we report the application results of these methods to chiral acetylene alcohols, together with the brief explanation of the CD exciton chirality method. As an extension of the results, we have developed a general methodology for determining the absolute configurations of acetylene alcohols having the HC≡CCH(OH)-moiety by combination of the *Sonogashira* reaction and the CD exciton chirality method.

The CD Exciton Chirality Method [2–4]

The exciton CD *Cotton* effects are observable, when two identical chromophores exhibiting intense π–π^* UV absorption are located in chiral positions with respect to each other, as exemplified by 1,2-diol bis(4-substituted benzoate) shown in Fig. 1(a). By the exciton coupling between two chromophores *i* and *j*, the excited state a splits into two energy levels, while the ground state 0 remains as a single level as shown in Fig. 1(b). The energy gap $2V_{ij}$ in the excited state is called the *Davydov* splitting. In consequence, there are two electronic transitions leading to two UV absorption bands.

The excitations to the two split energy levels give rise to CD *Cotton* effects of mutually opposite signs. As illustrated in Fig. 2, this leads to a CD spectrum with two component *Cotton* effects of opposite signs which are separated by the energy gap $\Delta\lambda$ ($=2V_{ij}$, *Davydov* splitting). Summation of the component *Cotton* effects results in the solid curve having two extrema. The extremum at longer wavelength is called the first *Cotton* effect, and the one at shorter wavelength is called the second *Cotton* effect. The amplitude *A* of split CD *Cotton* effects is defined as: $A = \Delta\varepsilon_1 - \Delta\varepsilon_2$, where $\Delta\varepsilon_1$ and $\Delta\varepsilon_2$ are intensities of the first and second *Cotton* effects. In the case of UV spectra, summation of two component spectra leads to a

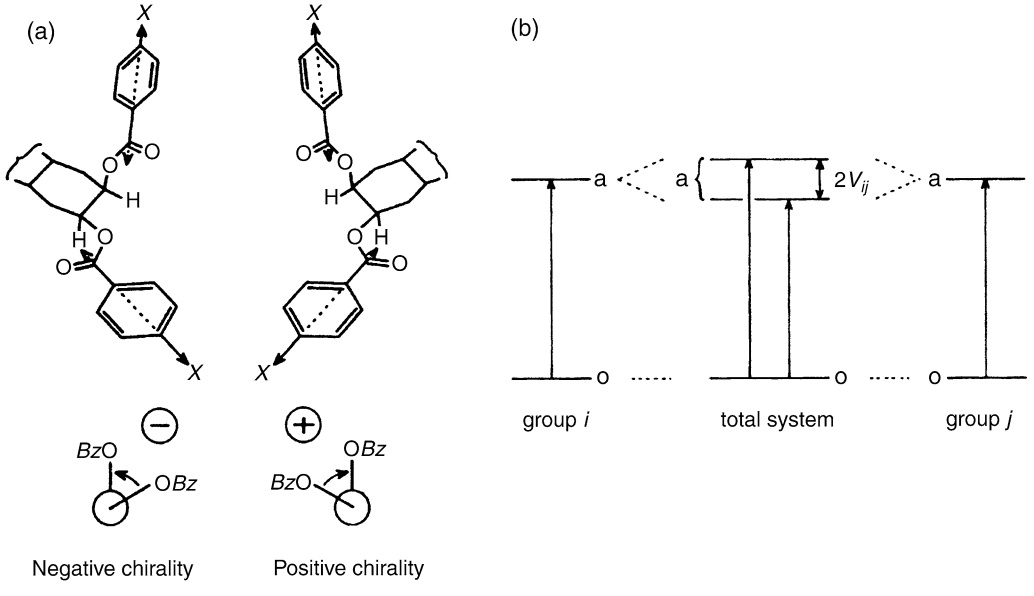


Fig. 1. (a) Exciton coupling between two identical chromophores (degenerate system), as exemplified by the system of 1,2-diol bis(4-substituted benzoate); (b) by the exciton coupling, the excited state splits into two energy levels; the energy gap $2V_{ij}$ is called *Davydov* splitting (adapted from Ref. [2])

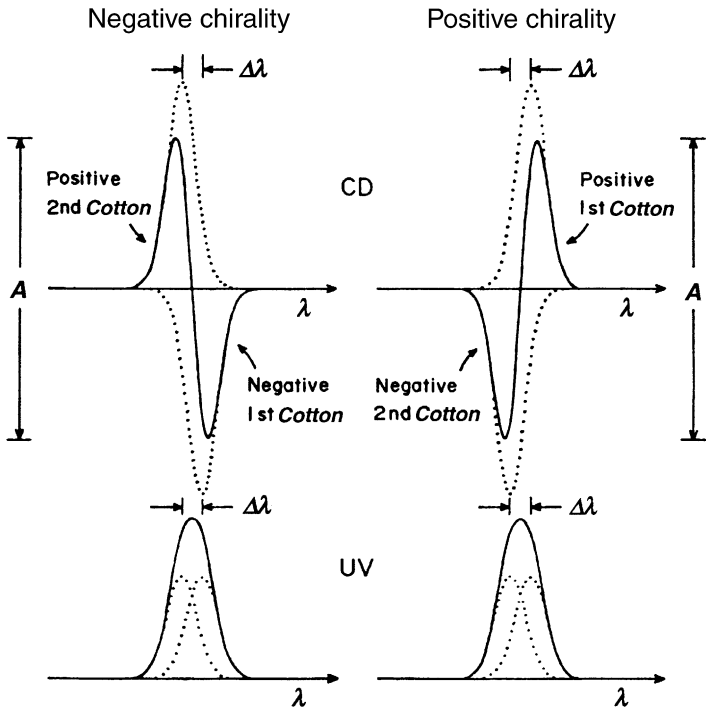


Fig. 2. Typical pattern of CD and UV spectra of exciton coupling system; summation of two component *Cotton* effects (dotted line) of opposite signs separated by *Davydov* splitting $\Delta\lambda$ yields CD and UV curves of solid line; positive chirality gives positive first and negative second CD *Cotton* effects, whereas negative chirality gives negative first and positive second *Cotton* effects; the amplitude (A) of split CD *Cotton* effects is defined as: $A = \Delta\varepsilon_1 - \Delta\varepsilon_2$ where $\Delta\varepsilon_1$ and $\Delta\varepsilon_2$ are intensities of first and second *Cotton* effects; in the case of UV spectra, summation of two component spectra leads to a single maximum (adapted from Ref. [2])

single maximum, because the energy gap $\Delta\lambda$ is relatively small compared to the bandwidth in most cases (Fig. 2).

Provided the electric transition dipole moments of the two chromophores constitute a clockwise screw sense (positive exciton chirality), as exemplified by the dibenzoate in the right side of Fig. 1, the sign of the first CD *Cotton* effect is positive and that of the second *Cotton* effect is negative (Fig. 2). When the two dipole moments make a counter-clockwise screw sense (negative exciton chirality: the dibenzoate in the left side of Fig. 1), the signs of the first and second *Cotton* effects are negative and positive. The exciton chirality governing the sign and amplitude of split *Cotton* effects is theoretically defined as: $\boldsymbol{R}_{ij} \cdot (\boldsymbol{\mu}_{i0a} \times \boldsymbol{\mu}_{j0a}) V_{ij}$, where $\boldsymbol{R}_{ij}$ is the interchromophoric distance vector from i to j, the symbol $\cdot$ denotes the scalar product of two vectors, $\boldsymbol{\mu}_{i0a}$ and $\boldsymbol{\mu}_{j0a}$ are electric transition dipole moment vectors of excitation $0 \rightarrow a$ of groups i and j, the symbol $\times$ denotes the vector product of two vectors, and V_{ij} is the interaction energy between two electric transition dipole moments, $\boldsymbol{\mu}_{i0a}$ and $\boldsymbol{\mu}_{j0a}$.

If the direction of the electric transition moment in the chromophore, *i.e.*, the polarization of the transition, is established, the signs of the observed two *Cotton* effects enable one to determine the absolute stereochemistry of the two chromophores in space. Namely, the absolute configuration of a target compound

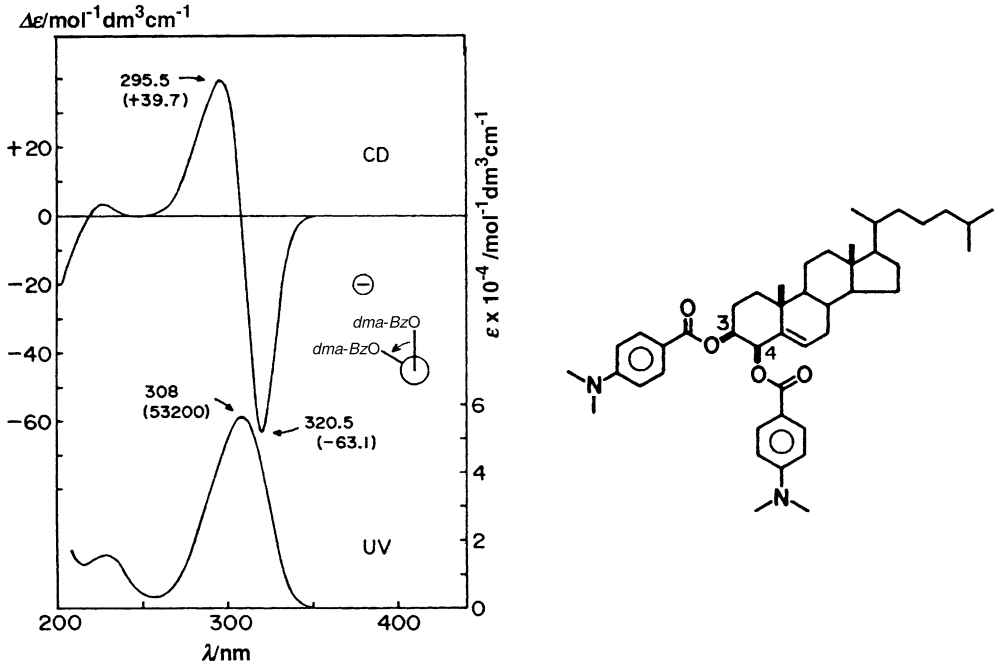


Fig. 3. CD and UV spectra of cholest-5-ene-3β,4β-diol bis(4-dimethylaminobenzoate) in *Et*OH (adapted from Ref. [2])

can be determined from the signs of CD *Cotton* effects on the basis of the chiral exciton coupling mechanism. Figure 3 shows a typical example of exciton coupling CD spectra observed in cholest-5-ene-3β,4β-diol bis(4-dimethylaminobenzoate). The 4-dimethylaminobenzoate chromophore exhibits an intense π–π^* UV band around 310 nm, which is polarized along the long axis of the chromophore. In the corresponding region, the CD spectrum shows negative first and positive second *Cotton* effects: $\lambda_{ext}(\Delta\varepsilon) = 320.5$ nm ($\Delta\varepsilon = -63.1$ mol^{-1}dm^3 cm^{-1}), 295.5 (+39.7), $A = -102.8$. The observed negative exciton chirality indicates the counterclockwise screw sense between the two long axes of the benzoate chromophores, leading to the (3*S*,4*R*) configuration in the steroidal skeleton. The absolute configuration of diol systems is thus determinable by the CD exciton chirality method.

The exciton coupling is the most effective in the case of a degenerate system having two identical chromophores, because the UV absorption maxima λ_{max} of both chromophores are the same. However, even in a nondegenerate system having two different chromophores, the CD spectrum is still governed by the exciton coupling mechanism. As shown in Fig. 4, the excited state has two energy levels, and the excitations to these levels give rise to exciton split CD *Cotton* effects as in the case of a degenerate case. For example, in the system of cholest-5-ene-3β,4β-diol 3-benzoate 4-(4-methoxybenzoate) shown in Fig. 5, the 257 nm transition of 4-methoxybenzoate and the 230 nm transition of benzoate couple with each other generating bisignate *Cotton* effects with typical pattern of exciton coupling, although their CD amplitude, *A*-value, is smaller than that of 3,4-dibenzoate (230/230 nm). The absolute configurations of nondegenerate system are thus determinable from the observed exciton CD spectra.

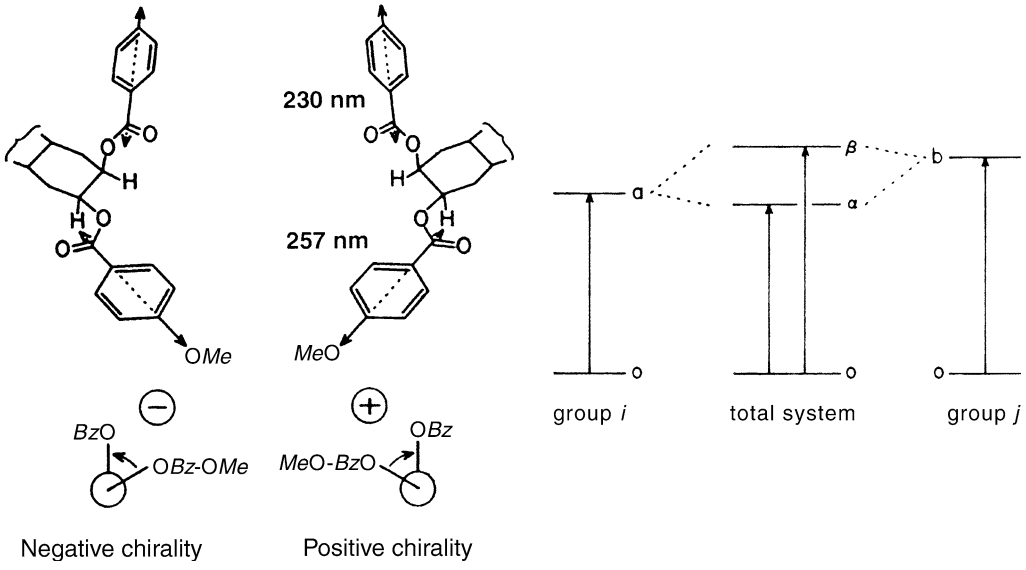


Fig. 4. (a) Exciton coupling between two nonidentical chromophores (nondegenerate system), as exemplified by the system of 1,2-diol 4-methoxybenzoate/benzoate (257 nm–230 nm); (b) the CD exciton chirality method is still applicable to the nondegenerate system composed of two different chromophores having similar UV λ_{max} values; namely, exciton split bisignate CD *Cotton* effects are observable, and the absolute configuration of the system can be determined (adapted from Ref. [2])

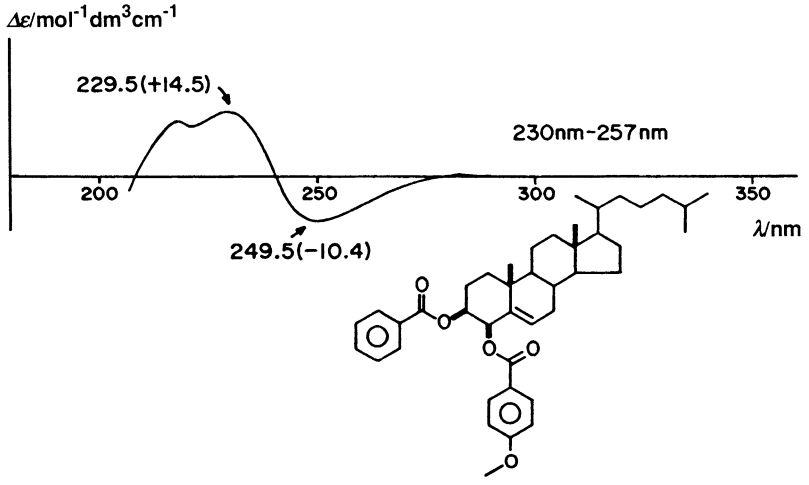


Fig. 5. CD spectrum of cholest-5-ene-3β,4β-diol 3-benzoate 4-methoxybenzoate in *Et*OH (adapted from Ref. [2])

The exciton chirality method is extensible to chiral compounds which already possess a chromophore suitable for exciton coupling. One typical example is shown in Fig. 6, where the original compound has a naphthalene chromophore which exhibits intense π–π^* transition at 226 nm polarized along the long axis of the chromophore. As a partner of exciton coupling, the unsubstituted benzoate was selected, because benzoate chromophore exhibits π–π^* transition at 230 nm polarized along the long axis of the chromophore. Namely in such a case, it is

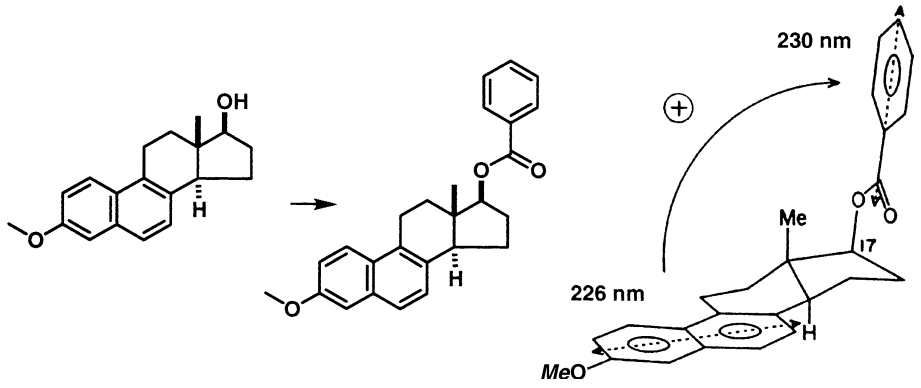


Fig. 6. Nondegenerate system having two different chromophores, where one chromophore is already present in the molecule in question: 226 nm transition of naphthalene chromophore polarized along the long axis and 230 nm transition of benzoate chromophore polarized along long axis; the two transition dipole moments constitute positive exciton chirality generating positive first and negative second *Cotton* effects (adapted from Ref. [2])

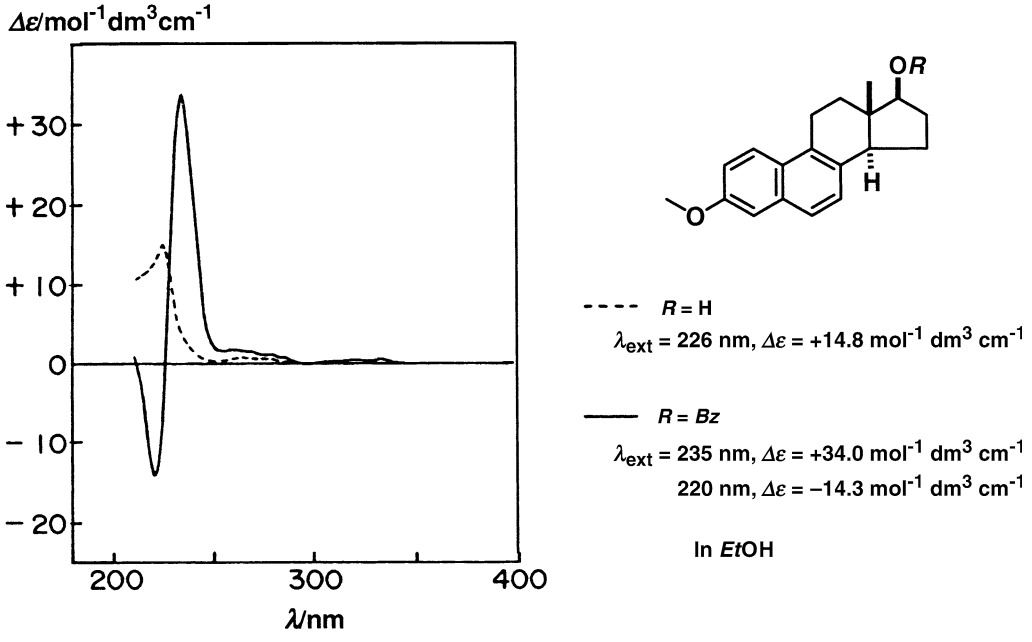


Fig. 7. CD spectra of estra-1,3,5,7,9-pentaene-3,17β-diol 3-methyl ether and its benzoate in *Et*OH (adapted from Ref. [2])

important to choose a chromophore having λ_{max} similar to that of the chromophore contained in the molecule. As expected, the exciton coupling between naphthalene and benzoate chromophores generates intense exciton split CD *Cotton* effects (Fig. 7), from which the absolute configuration of the original compound is determinable.

In this paper, we report the application of the CD exciton chirality method to phenylacetylene alcohol benzoates, where phenylacetylene and benzoate chromophores effectively couple with each other (Fig. 8). From the exciton CD data, the absolute configurations of original phenylacetylene alcohols were determined.

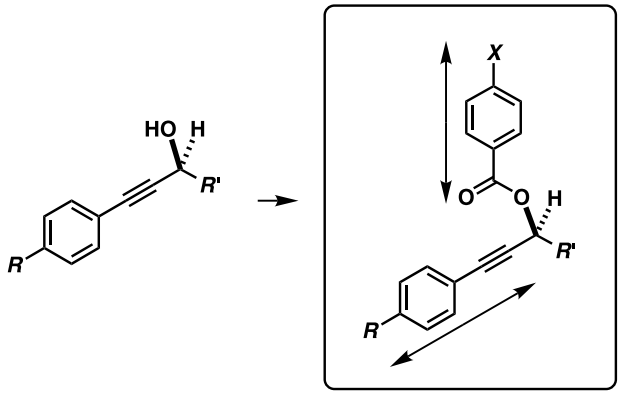


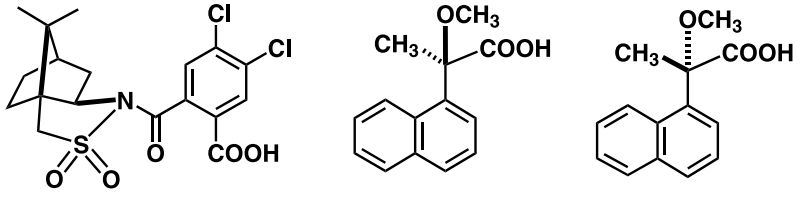
Fig. 8. Application of the CD exciton chirality method to nondegenerate systems of phenylacetylene alcohol benzoates

Furthermore, by combining with the *Sonogashira* reaction, a novel methodology for determining the absolute configurations of acetylene alcohols having the HC≡CCH(OH)-moiety was developed as described below.

Results and Discussion

Preparation of Enantiopure Phenylacetylene Alcohols

We have previously reported that the chiral acids listed in Fig. 9 are very powerful for enantioresolution of racemic alcohols and also for determination of their absolute configurations [5, 6, 13, 14]. Namely, camphorsultam dichlorophthalic acid (*CSDP* acid) (1*S*,2*R*,4*R*)-(−)-**1** was condensed with racemic alcohols to yield diastereomeric esters, which were easily separated by HPLC on silica gel. In general, the *CSDP* esters have high probability to crystallize as large single crystals suitable for X-ray diffraction experiments. Therefore their stereostructures were determined by X-ray crystallography. Since the absolute configuration of *CSDP* acid is already known, the absolute configuration of the alcohol part was easily determined from the ORTEP drawing of X-ray analysis. From the *CSDP* esters, enantiopure alcohols were recovered by hydrolysis or solvolysis [5, 6].



***CSDP* acid**
(1*S*,2*R*,4*R*)-(–)-1

***MαNP* acid**
(*R*)-(–)-2

***MαNP* acid**
(*S*)-(+)-2

Fig. 9. Chiral molecular tools for preparation of enantiopure alcohols and determination of absolute configurations

Another method is to use 2-methoxy-2-(1-naphthyl)propionic acids (*MαNP* acids) (*R*)-(−)-**2** and (*S*)-(+)-**2** [13–15]. For example, racemic alcohol was esterified with *MαNP* acid (*S*)-(+)-**2**, and the diastereomeric esters obtained were easily separated by HPLC on silica gel. By applying the ^{1}H NMR anisotropy method of *MαNP* acid to diastereomeric esters, their absolute configurations were empirically determined. From the *MαNP* esters, enantiopure alcohols were recovered by solvolysis [13, 14].

The *MαNP* acid method is also useful for determination of absolute configurations of chiral alcohols, as exemplified below. Namely, chiral alcohol was condensed with *MαNP* acid (*R*)-(−)-**2** and also with (*S*)-(+)-**2**. From the ^{1}H NMR anisotropy data of both *MαNP* esters, the absolute configuration of the original alcohol was determined [13, 14].

As target compounds, the enantiopure phenylacetylene alcohols (**3**–**6**, **8**, **10**) listed in Fig. 10 were synthesized; alcohol (*S*)-(−)-**3** had been previously prepared by the *MαNP* acid method, and its absolute configuration also had been determined by the ^{1}H NMR anisotropy method [13o]. For alcohols **4**, **5**, and **6**, racemic alcohols were synthesized as shown in Scheme 1; all reactions proceeded well in good yields. To enantioresolve racemic alcohol **4**, we have first tried to use the *MαNP* acid method. However, it was difficult to separate diastereomeric *MαNP* esters formed from alcohol **4**. Instead, we have applied the *CSDP* acid method as shown in Scheme 2; alcohol (±)-**4** was esterified with *CSDP* acid (1*S*,2*R*,4*R*)-(−)-**1**, 4-dimethylaminopyridine (*DMAP*), and 1,3-dicyclohexylcarbodiimide

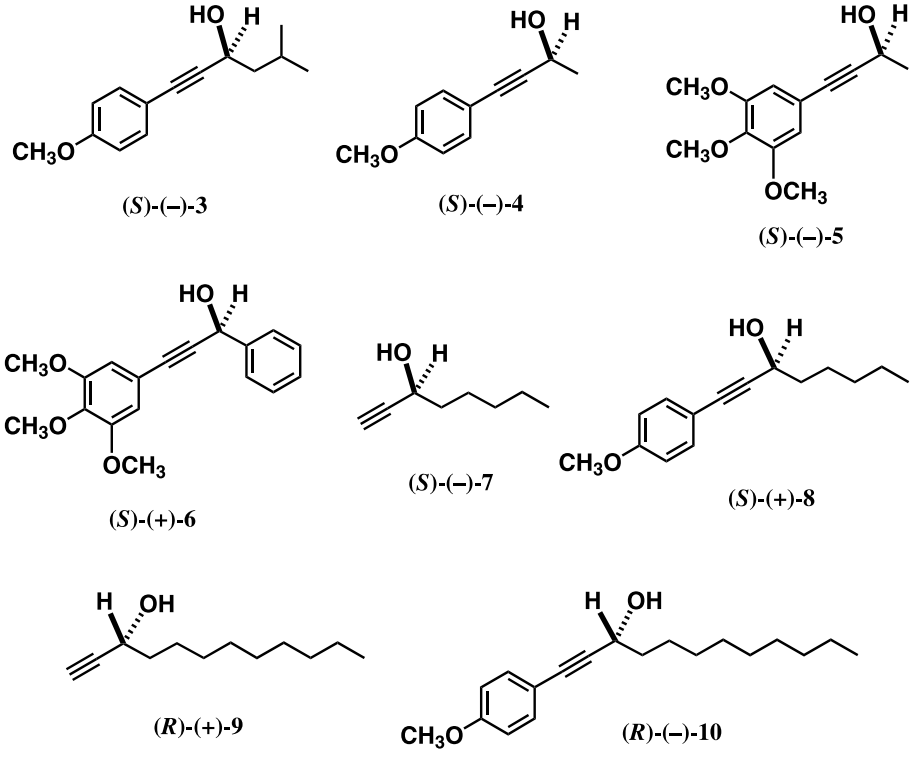
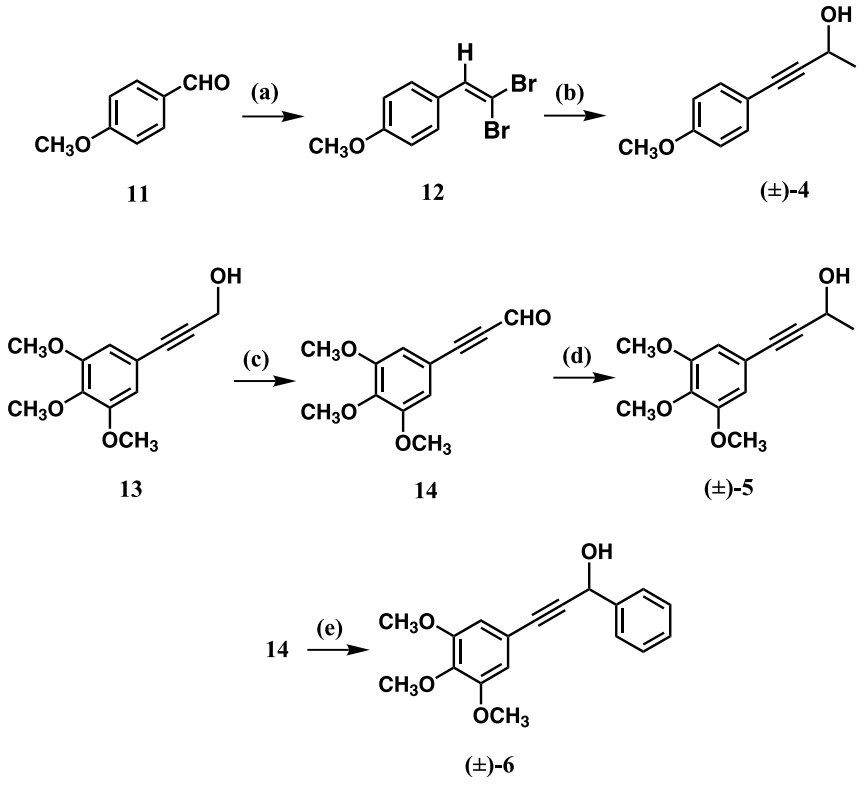


Fig. 10. Chiral acetylene alcohols and their absolute configurations

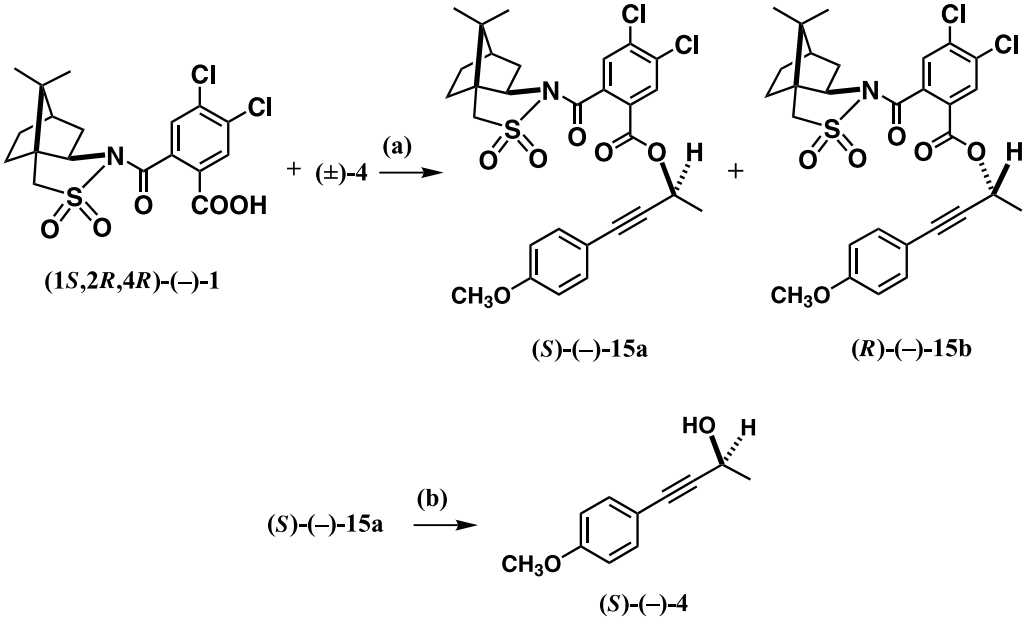


(a) CBr_4, P*Ph*$_3$/CH_2Cl_2, rt, **12**, 99%; (b) *n-Bu*Li/*THF*, –78°C and then CH_3CHO, –78°C - rt, (±)-**4**, 79%; (c) *PDC*/CH_2Cl_2, rt, **14**, 65%; (d) *Me*MgBr/*THF*, 0°C - rt, (±)-**5**, 95%; (e) *Ph*MgBr/*THF*, 0°C - rt, (±)-**6**, 84%

Scheme 1

(*DCC*) yielding diastereomeric esters, which were separated by HPLC on silica gel: *n*-hexane/*Et*O*Ac* 3/1, $\alpha = 1.06$, *R*s = 0.82 (Table 1). In this case, it was not easy to separate diastereomeric esters, because of small α value. However, we performed HPLC separation several times to obtain enough amounts of both esters: the first-eluted ester (−)-**15a**, 49%, and the second-eluted ester (−)-**15b**, 46%. To apply the X-ray crystallographic analysis, those esters were subjected to crystallization; however, both compounds were obtained as amorphous solids. The first-eluted ester (−)-**15a** was treated with K_2CO_3 in *Me*OH yielding enantiopure alcohol (−)-**4**.

The *CSDP* acid method was similarly applied to racemic alcohols **5** and **6**. The esters formed from alcohol (±)-**5** were separated by HPLC on silica gel in a moderate extent: *n*-hexane/*Et*O*Ac* 3/1, $\alpha = 1.13$, *R*s = 1.75 (Table 1). The first-eluted ester (*S*)-(−)-**16a** was subjected to solvolysis giving enantiopure alcohol (*S*)-(−)-**5** (Scheme 3). Alcohol (±)-**6** was esterified with *CSDP* acid yielding a diastereomeric mixture, which was separated by HPLC on silica gel: *n*-hexane/*Et*O*Ac* 2/1, $\alpha = 1.08$, *R*s = 1.26 (Table 1). The first-eluted ester (*S*)-(−)-**17a** was treated with K_2CO_3 in *Me*OH giving enantiopure alcohol (+)-**6** (Scheme 3).



Preparation of *CSDP* esters and recovery of chiral acetylene alcohol: (a) *DCC*, *DMAP*, CH_2Cl_2, rt, (*S*)-(–)-**15a**, 49%, (*R*)-(–)-**15b**, 46%; (b) K_2CO_3/*Me*OH, rt, (*S*)-(–)-**4**, 83%

Scheme 2

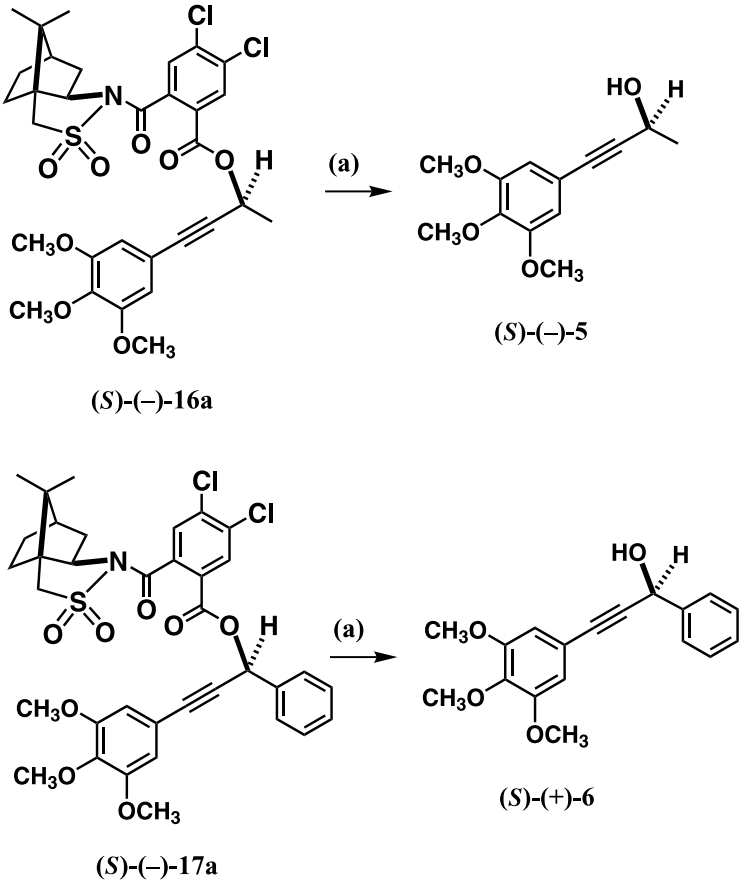
Table 1. Silica gel-HPLC separation of diastereomeric esters formed from racemic acetylene alcohols with (−)-*CSDP* acid, recovery of chiral alcohols, and determination of their absolute configurations by the ^{1}H NMR anisotropy method

Acid	Alcohol	Solvent[a]	α	*Rs*	Ester (1st Fr.)	Chiral alcohol (from 1st Fr.)	^{1}H NMR $\Delta\delta$[b]
(−)-**1**	(±)-**4**	*H*/*EA* = 3/1	1.06	0.82	(*S*)-(−)-**15a**	(*S*)-(−)-**4**	*yes*[c]
(−)-**1**	(±)-**5**	*H*/*EA* = 3/1	1.13	1.75	(*S*)-(−)-**16a**	(*S*)-(−)-**5**	*yes*[c]
(−)-**1**	(±)-**6**	*H*/*EA* = 2/1	1.08	1.26	(*S*)-(−)-**17a**	(*S*)-(+)-**6**	*yes*[c]

[a] *H* = *n*-hexane, *EA* = ethyl acetate; [b] $\Delta\delta$ = ^{1}H NMR anisotropy effect; [c] absolute configuration determined by the ^{1}H NMR anisotropy method agreed with that by the CD exciton chirality method

Determination of the Absolute Configurations of Phenylacetylene Alcohols by the ^{1}H NMR Anisotropy Method

To determine the absolute configurations of the phenylacetylene alcohols obtained, we have next applied the ^{1}H NMR anisotropy method using *MαNP* acids (*R*)-(−)-**2** and (*S*)-(+)-**2**. The general procedure of the method is summarized as follows (Fig. 11); i) chiral alcohol, whose unknown absolute configuration is defined as *X*, is esterified with (*R*)-*MαNP* acid and (*S*)-*MαNP* acid separately; ii) the ^{1}H NMR spectra of (*R*,*X*)- and (*S*,*X*)-esters are measured, and the chemical shift data of alcohol moieties in each ester are obtained as $\delta(R,X)$ and $\delta(S,X)$; iii) the chemical



Recovery of chiral acetylene alcohols: (a) K_2CO_3/*Me*OH, rt, (*S*)-(–)-**5**, 84%, (*S*)-(+)-**6**, 87%

Scheme 3

shift difference values are calculated as $\Delta\delta = \delta(R,X) - \delta(S,X)$; iv) in the projection of the sector rule shown in Fig. 11, the group R^1 with protons exhibiting positive $\Delta\delta$ values is placed in the right sector and the group R^2 with protons showing negative $\Delta\delta$ values in the left sector. In the sector rule, the *OMαNP* group is located in the down and front side, and the methine proton of the secondary alcohol in the down and rear side. From this projection, the absolute configuration *X* of chiral alcohol can be determined [13, 14].

This ^{1}H NMR anisotropy method using *MαNP* acid is based on the anisotropy effect of the naphthyl group generated by the ring current induced under the external magnetic field. The *MαNP* esters take preferred conformations as shown in Fig. 11, where the ester carbonyl oxygen atom is *synperiplanar* (*syn*) to the O*Me* group in *MαNP* acid moiety and also to the methine proton of the secondary alcohol. Therefore in the (*R*,*X*)-ester, the group R^2 faces the naphthyl group and hence the proton NMR signals of group R^2 are moved to a higher magnetic field (high field shift). On the other hand, the group R^1 faces the naphthyl group in the (*S*,*X*)-ester,

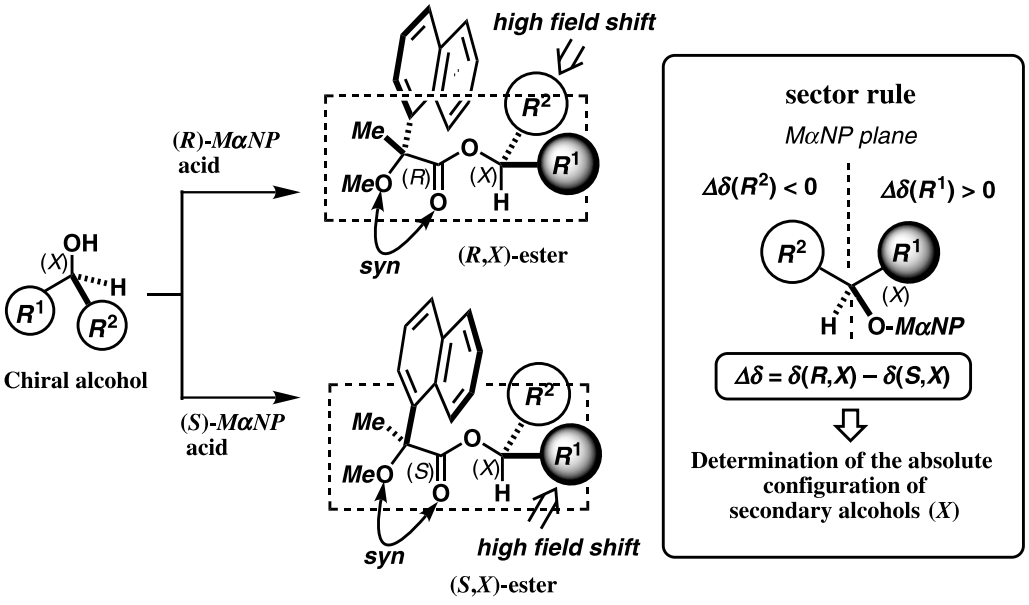
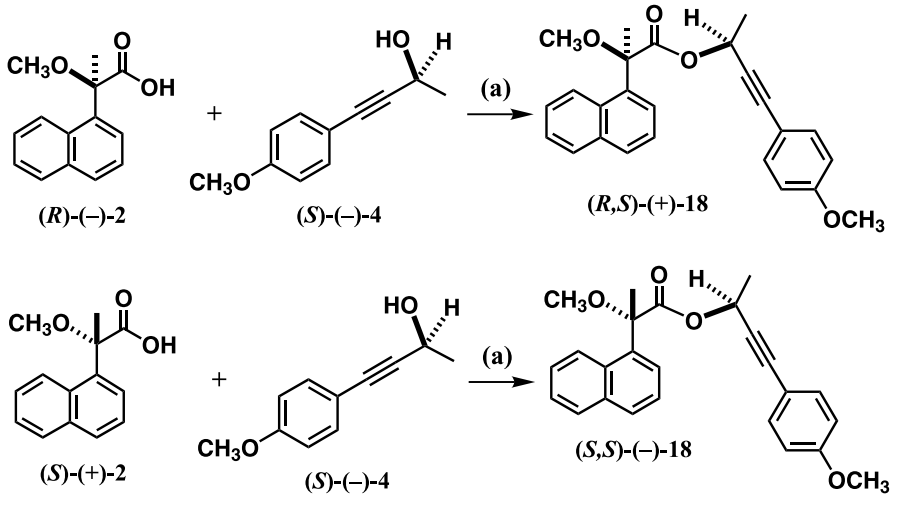


Fig. 11. The ^{1}H NMR anisotropy method using *MαNP* acid for determining the absolute configuration of chiral alcohols

leading to high field shift. The group R^1 thus takes positive $\Delta\delta$ values, while the group R^2 takes negative $\Delta\delta$ values. Based on this mechanism, the absolute configuration of a chiral alcohol is determinable. The ^{1}H NMR anisotropy method using *MαNP* acid is an empirical rule, but it is very useful and extensively applicable to various chiral secondary alcohols [13, 14].



Preparation of *MαNP* esters: (a) *DCC*, *DMAP*, CH_2Cl_2, rt-34°C, 86–97%

Scheme 4

The application of the *MαNP* acid method to chiral phenylacetylene alcohol (−)-**4** was executed as follows. Chiral alcohol (*X*)-(−)-**4** was esterified with *MαNP* acids (*R*)-(−)-**2** and (*S*)-(+)-**2** yielding esters (*R*,*X*)-(+)-**18** and (*S*,*X*)-(−)-**18** (Scheme 4). Their ^{1}H NMR signals of alcohol part were easily assigned and then $\Delta\delta$ ($=\delta((R,X)\text{-}\mathbf{18}) - \delta((S,X)\text{-}\mathbf{18})$) values were calculated as shown in Fig. 12. Since the *ortho*- and *meta*-protons of phenyl group show positive $\Delta\delta$ values, +0.15 and +0.03, the 4-methoxyphenylacetylene group was placed in the right side. On the other hand, the methyl group protons exhibit a negative $\Delta\delta$ value, −0.21, and therefore it was placed in the left side. So, the absolute configuration of alcohol (−)-**4** was explicitly determined as $X = S$. The observed $\Delta\delta$ values are distributed in

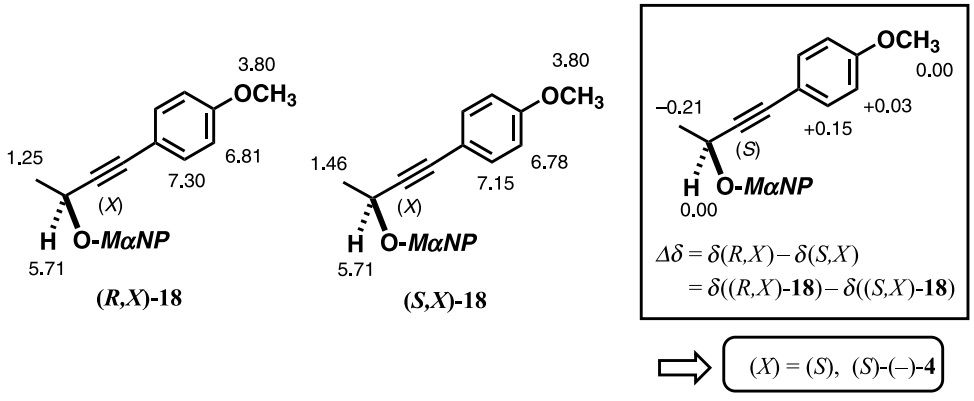
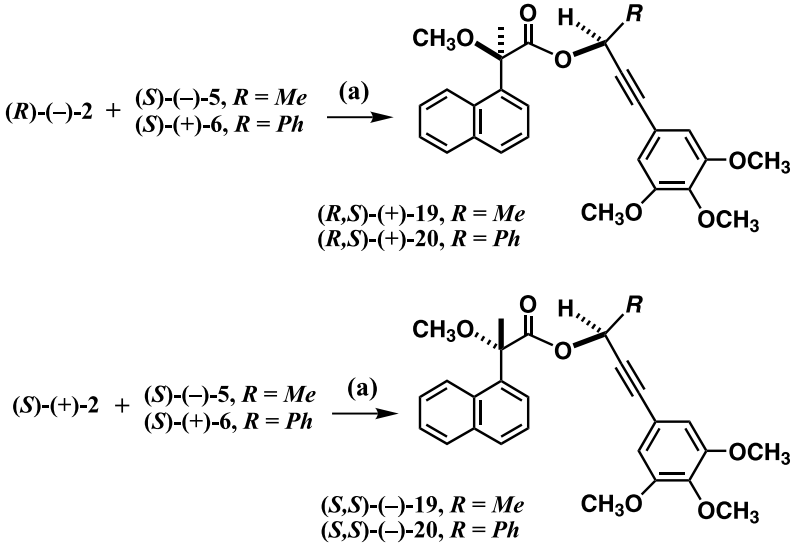


Fig. 12. ^{1}H NMR chemical shifts of *MαNP* esters (*R*,*X*)-**18** and (*S*,*X*)-**18**, and $\Delta\delta$ values leading to the absolute configuration of the chiral alcohol, $X = S$, *i.e.* (*S*)-(−)-**4**



Preparation of *MαNP* esters: (a) *DCC*, *DMAP*, CH_2Cl_2, rt-34°C, 86–99%

Scheme 5

a reasonable manner; more remote protons from the *OMαNP* group show smaller $\Delta\delta$ values. The distribution pattern indicates that the determination of the absolute configuration of (−)-**4** is reliable.

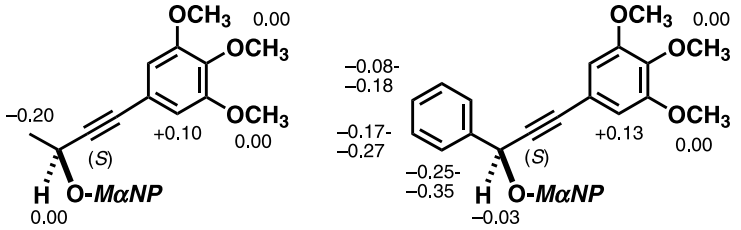


Fig. 13. $\Delta\delta$ Values leading to the absolute configuration of the chiral alcohol, $X = S$, *i.e.* (*S*)-(−)-**5** and (*S*)-(+)-**6**

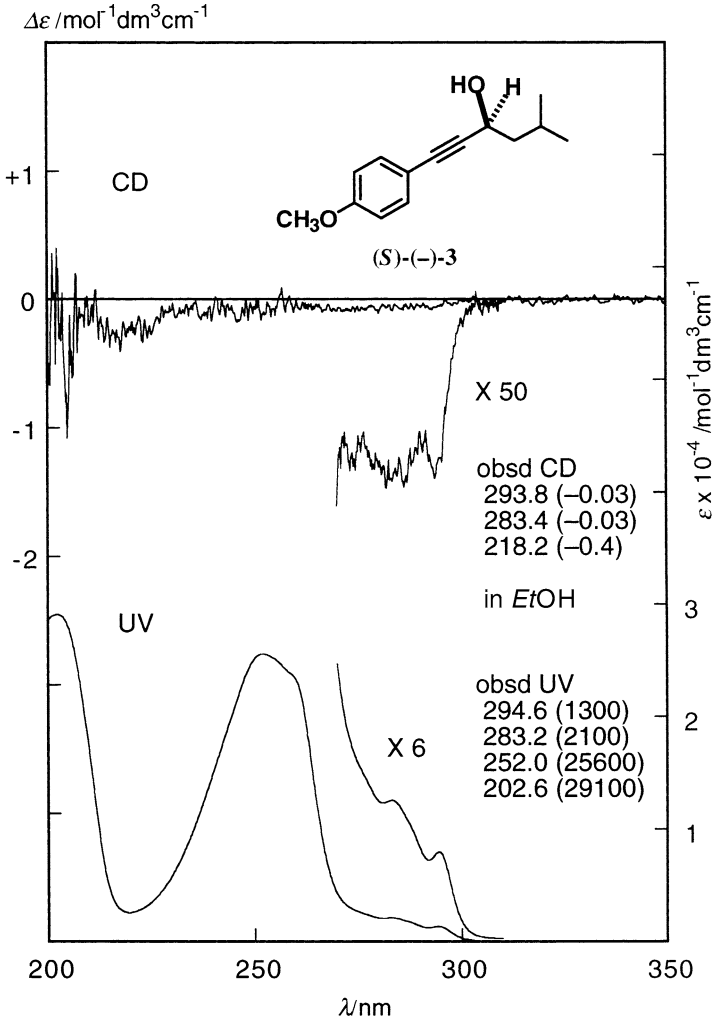


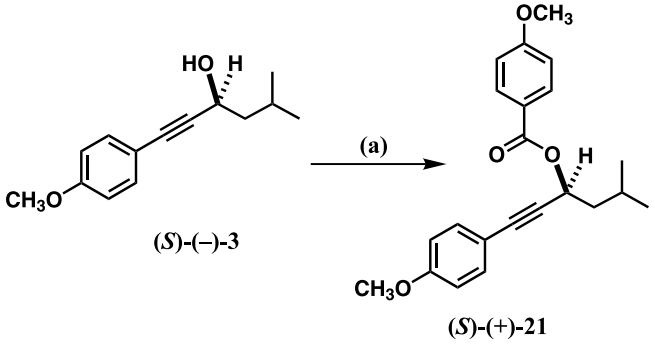
Fig. 14. CD and UV spectra of alcohol (*S*)-(−)-**3** in *Et*OH

The remaining alcohols (−)-**5** and (+)-**6** were similarly converted to *MαNP* esters (Scheme 5) and then $\Delta\delta$ values were calculated as shown in Fig. 13; the $\Delta\delta$ values of *MαNP* esters **19** are similar to those of **18** leading to the (*S*) absolute configuration of alcohol (−)-**5**. In the case of *MαNP* esters **20**, the phenyl group shows negative $\Delta\delta$ values, while 3,4,5-trimethoxyphenylacetylene group shows a positive $\Delta\delta$ value, indicating the (*S*) absolute configuration of alcohol (+)-**6**.

Determination of the Absolute Configurations of Phenylacetylene Alcohols by the CD Exciton Chirality Method

Next the CD exciton chirality method was applied to phenylacetylene alcohols **3**–**6** to determine their absolute configurations. Figure 14 illustrates the CD and UV spectra of (−)-**3**; the 4-methoxyphenylacetylene group exhibits intense UV absorption band of π–π^* transition at 252 nm ($\varepsilon = 25600\,\mathrm{mol^{-1}\,dm^3\,cm^{-1}}$), which is polarized along the long axis of the chromophore [16]. Although the 252 nm transition is allowed, it is almost silent in the CD spectrum of (−)-**3**. To generate the most effective exciton split CD *Cotton* effects, the 4-methoxybenzoate chromophore having a π–π^* transition at 257 nm was selected, because the λ_{max} value of 4-methoxybenzoate is close to that of 4-methoxyphenylacetylene chromophore. So 4-methoxybenzoate (+)-**21** was prepared (Scheme 6) and its CD and UV spectra were measured as shown in Fig. 15. As expected, the CD spectrum of (+)-**21** shows very intense bisignate *Cotton* effects due to the exciton coupling between 4-methoxyphenylacetylene and 4-methoxybenzoate chromophores: $\lambda_{ext} = 266.0$ nm ($\Delta\varepsilon = +30.9\,\mathrm{mol^{-1}\,dm^3\,cm^{-1}}$), 246.4 (−22.7), $A = +53.6$. The positive first and negative second *Cotton* effects observed indicate the positive exciton chirality between the two chromophores.

The preferred conformation of benzoate (*S*)-**21** is depicted in Fig. 16, where the carbonyl oxygen atom of benzoate group is *synperiplanar* (*syn*) to the alcohol methine proton. The 257 nm transition of 4-methoxybenzoate is polarized along the long axis of the chromophore, and the 252 nm of 4-methoxyphenylacetylene is



(a) 4-Methoxybenzoic acid, *DCC*, *DMAP*, CH_2Cl_2, rt, (*S*)-(+)-**21**, 98%

Scheme 6

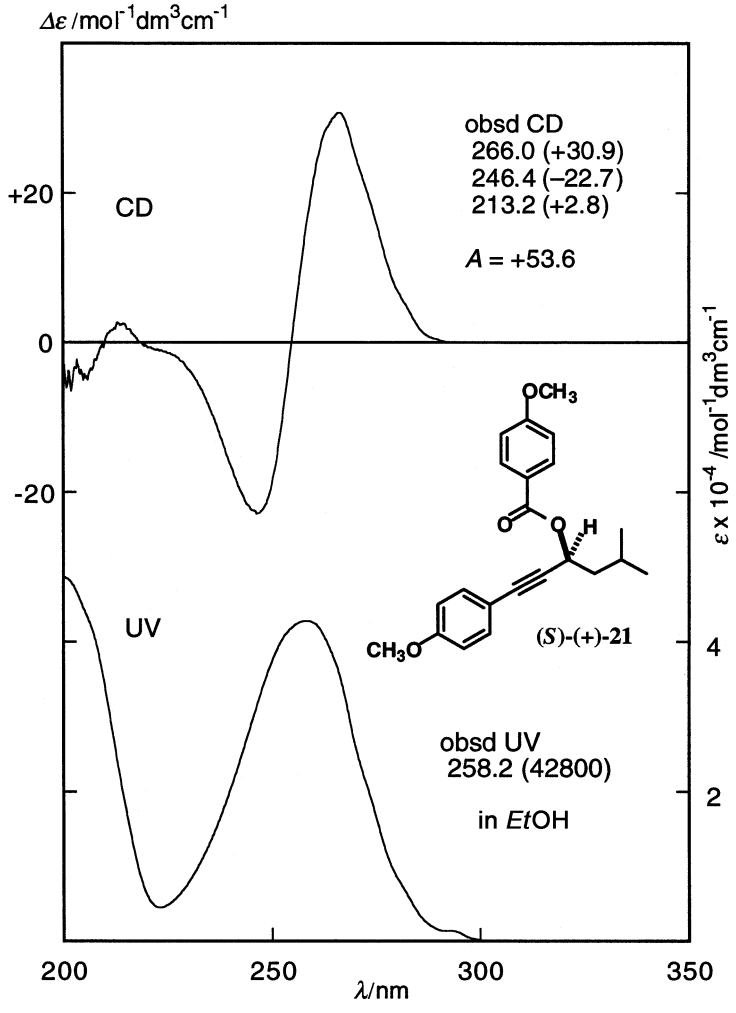
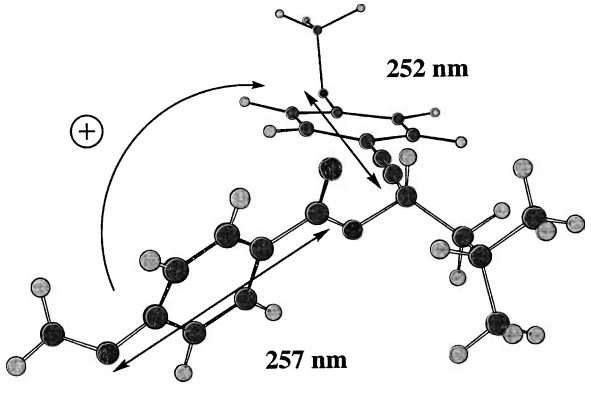


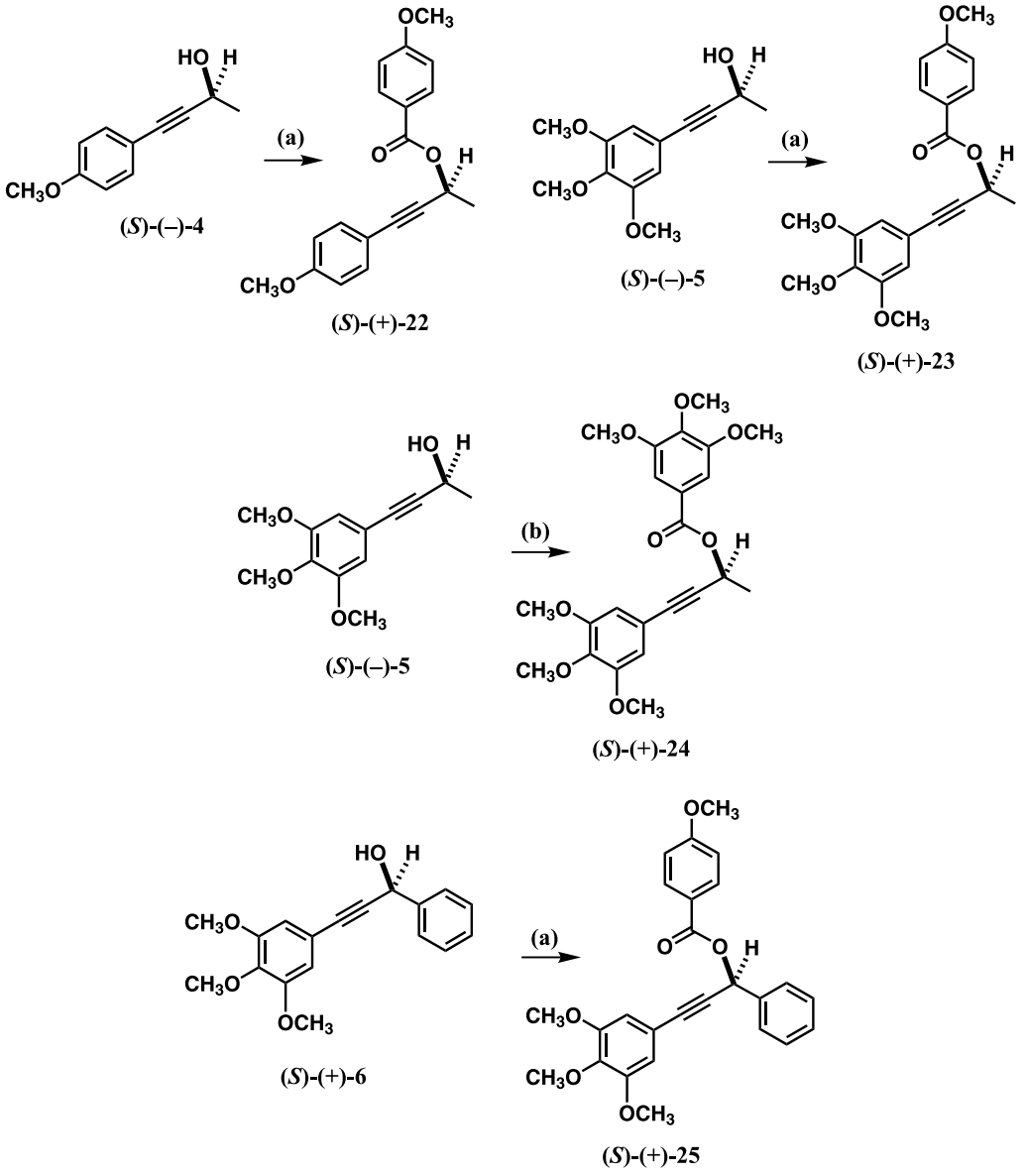
Fig. 15. CD and UV spectra of benzoate (*S*)-(+)-**21** in *Et*OH



(*S*)-(+)-**21**

Fig. 16. Positive exciton chirality between two long axes of 4-methoxybenzoate and 4-methoxyphenylacetylene chromophores

also polarized along the long axis of the group as illustrated in Fig. 16. Since the 4-methoxyphenylacetylene group is linear in its form, the direction of the transition moment is invariant, even if the phenylacetylene group rotates around C–C single bonds. In the stereostructure of (*S*)-**21**, the long axis of 4-methoxybenzoate is located in the front side and that of 4-methoxyphenylacetylene is in the rear side. Namely, the two long axes constitute a clockwise screw sense, *i.e.*, positive



(a) 4-Methoxybenzoic acid, *DCC*, *DMAP*, CH_2Cl_2, rt, 87–99%;
(b) 3,4,5-trimethoxybenzoic acid, *DCC*, *DMAP*, CH_2Cl_2, rt, 96%

Scheme 7

exciton chirality. Therefore the observed bisignate *Cotton* effects of positive exciton chirality lead to the (*S*) absolute configurations of ester (+)-**21** and alcohol (−)-**3**, which agree with the previous determination by the ^{1}H NMR anisotropy method.

Other phenylacetylene alcohols **4**–**6** were similarly converted to benzoates **22**–**25** (Scheme 7). In the case of benzoate (+)-**22**, its CD spectrum exhibits positive first and negative second *Cotton* effects leading to the (*S*) absolute configuration (Fig. 17). Its *A*-value is comparable to that of (+)-**21** indicating that the CD sign and intensity are mostly governed by the exciton coupling between 4-methoxybenzoate and 4-methoxyphenylacetylene groups, and the contribution of aliphatic side chain is relatively small. Benzoate (+)-**23** is a unique compound having 3,4,5-trimethoxyphenylacetylene chromophore; although its CD spectrum shows bisignate *Cotton* effects of positive exciton chirality leading to the (*S*) absolute

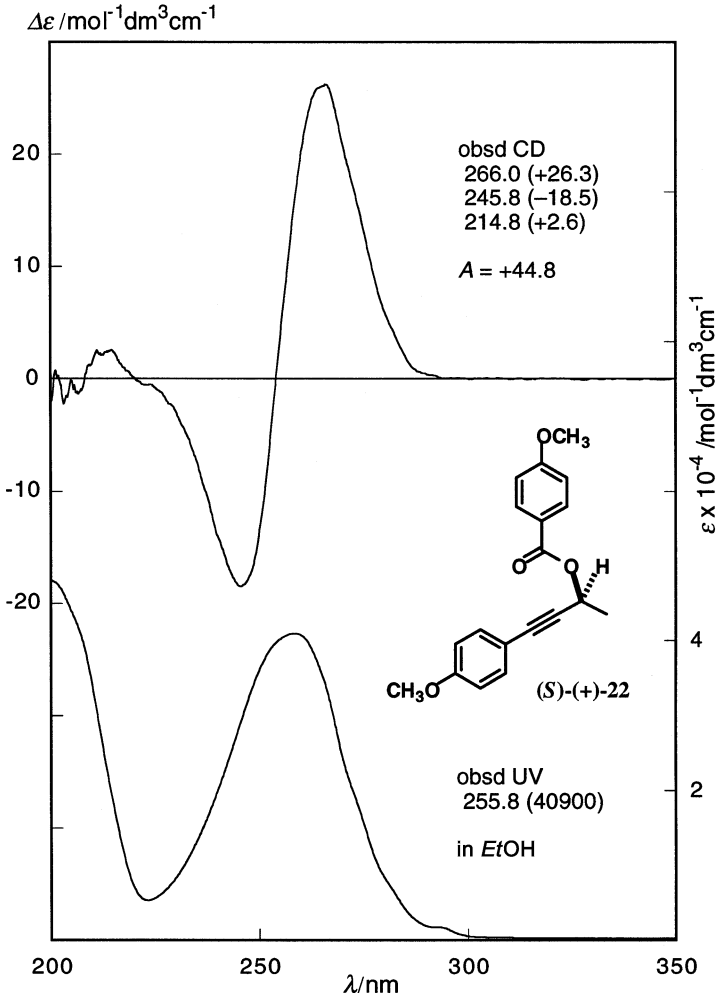


Fig. 17. CD and UV spectra of benzoate (*S*)-(+)-**22** in *Et*OH

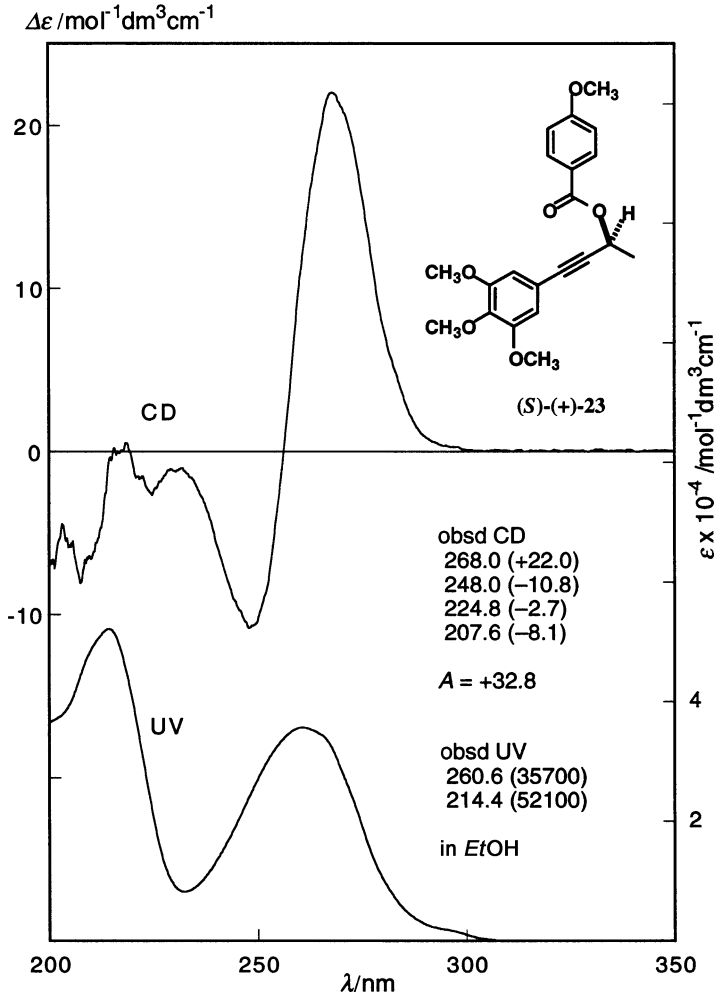


Fig. 18. CD and UV spectra of benzoate (*S*)-(+)-**23** in *Et*OH

configuration, its *A*-value is smaller than those of 4-methoxyphenylacetylene/4-methoxy-benzoates **21** and **22** (Fig. 18). It may be interpreted as follows; two methoxyl groups at the 3- and 5-positions weaken the long-axis polarized transition of the phenylacetylene chromophore as judged from the UV data of alcohol (*S*)-(−)-**5**, $\lambda_{max} = 265.2\,nm$ ($\varepsilon = 15700\,mol^{-1}\,dm^3\,cm^{-1}$) (see Experimental Section), and hence the exciton coupling CD becomes weaker. This effect is more emphasized in the CD spectrum of **24**; its *A*-value is *ca.* one third of that of **22** (Fig. 19). Therefore, chromophores having substituents, which strengthen the long-axis polarized transition, are more appropriate for the CD exciton chirality method. Compound **25** is also unique in the sense that it has the third chromophore in addition to a pair of the exciton coupling chromophores; it may be worried that the third phenyl chromophore disturbs the exciton coupling between 4-methoxybenzoate and 3,4,5-trimethoxyphenylacetylene groups. However, the CD spectrum of (+)-**25** shows a clear pattern of positive exciton chirality leading to the (*S*) absolute configuration (Fig. 20). The *A*-value of (+)-**25** is almost

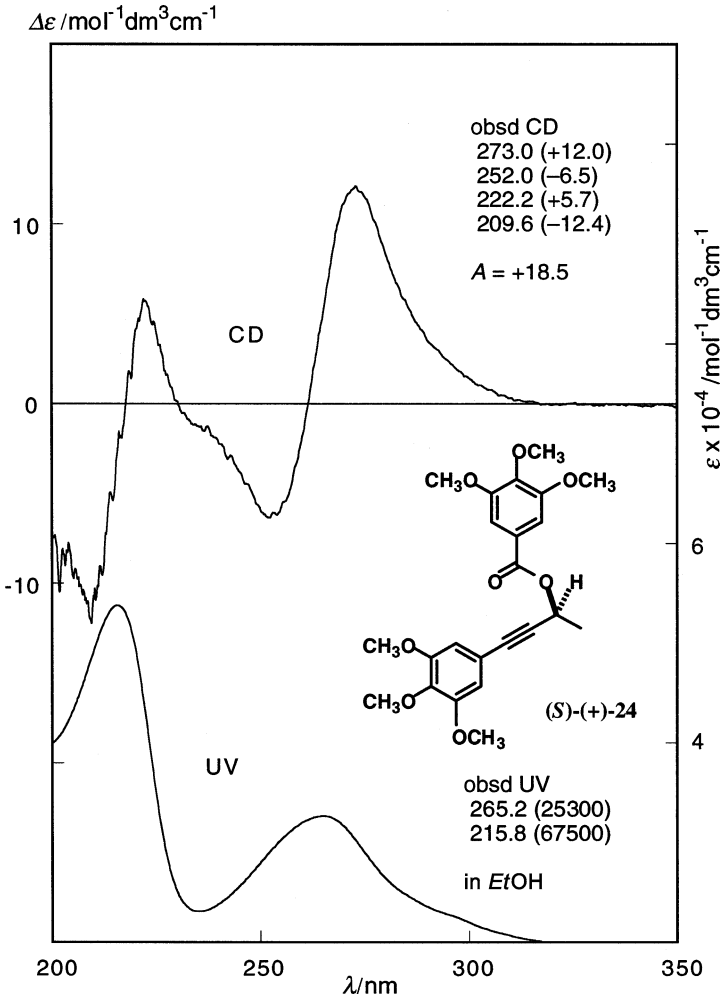


Fig. 19. CD and UV spectra of benzoate (*S*)-(+)-**24** in *Et*OH

comparable to that of (+)-**23** indicating that the contribution of phenyl group is relatively small.

Determination of the Absolute Configurations of Acetylene Alcohols by Combination of the Sonogashira Reaction and the CD Exciton Chirality Method

As discussed above, the CD exciton chirality method is useful for determining the absolute configuration of phenylacetylene alcohols. As an extension of the results, we have developed a general methodology for determining the absolute configurations of chiral acetylene alcohols having the HC≡CCH(OH)-moiety by combination of the *Sonogashira* reaction and the CD exciton chirality method as shown in Fig. 21. To determine the absolute configuration of acetylene alcohols, the CD exciton chirality method had been applied to their benzoates [17]. However, it is difficult to observe bisignate CD *Cotton* effects due to the exciton coupling between acetylene and benzoate chromophores, because the π–π^* transition of

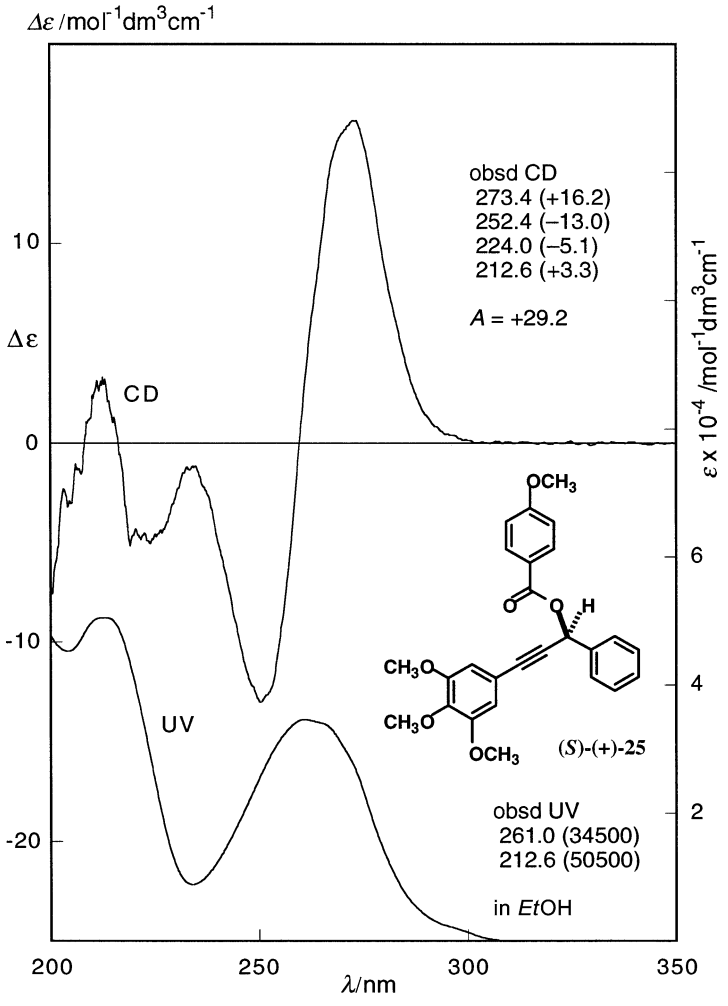


Fig. 20. CD and UV spectra of benzoate (*S*)-(+)-**25** in *Et*OH

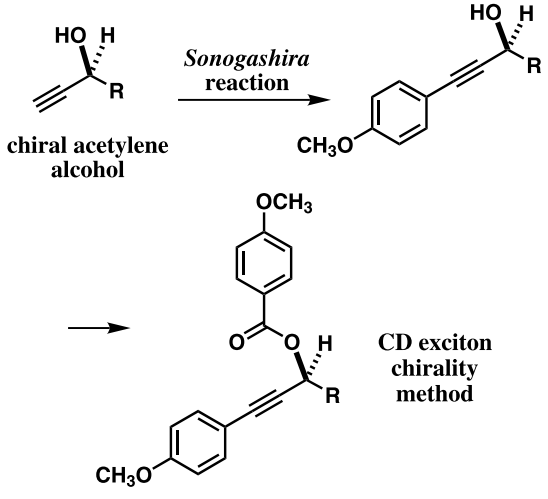
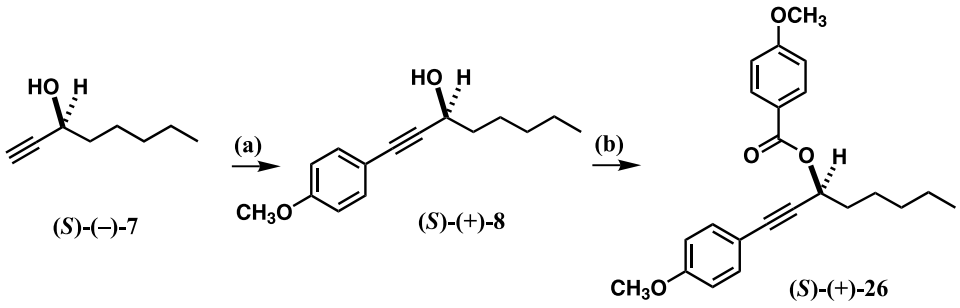


Fig. 21. A general methodology for determining the absolute configuration of acetylene alcohols by combination of the *Sonogashira* reaction and the CD exciton chirality method



(a) 4-Iodoanisole, CuI, Et_3N, $PdCl_2(PPh_3)_2$, rt, 78%;
(b) 4-methoxybenzoic acid, *DCC*, *DMAP*, CH_2Cl_2, rt, 99%

Scheme 8

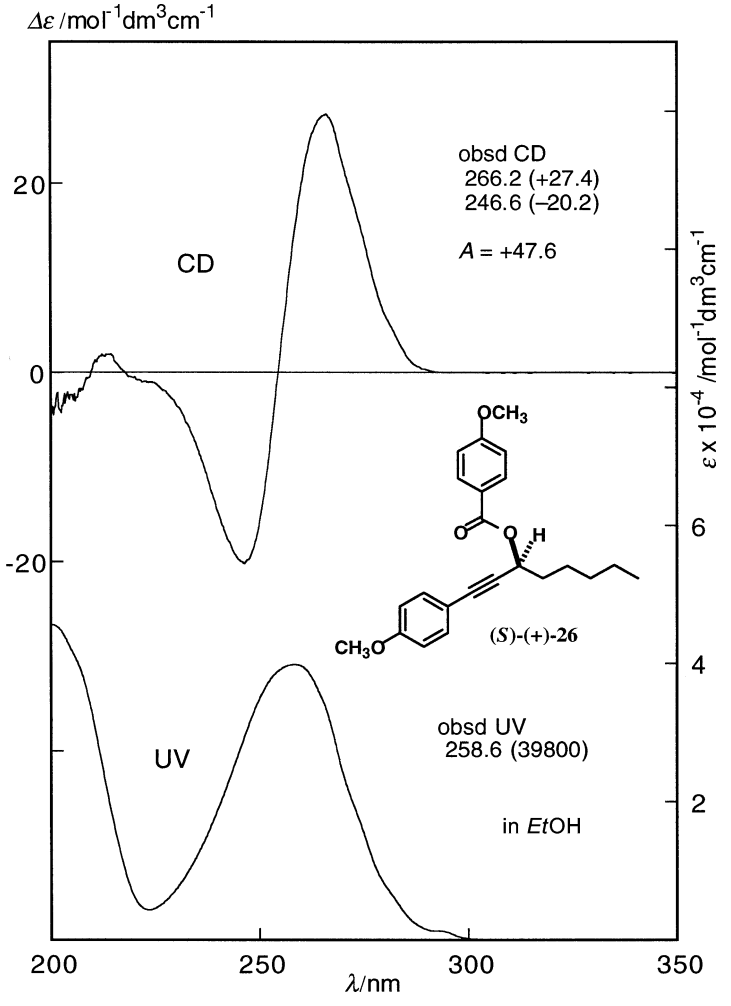
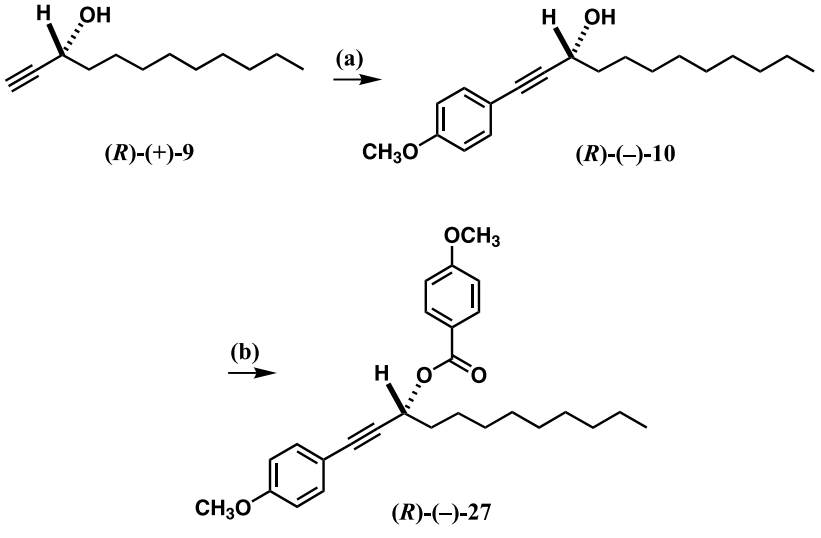


Fig. 22. CD and UV spectra of benzoate (*S*)-(+)-**26** in *Et*OH

acetylene triple bond is located below 180 nm. To observe the ideal exciton split *Cotton* effects necessary for the unambiguous determination of absolute configuration, we have taken the strategy to convert the acetylene group to 4-methoxyphenylacetylene moiety by the *Sonogashira* reaction (Fig. 21) [18, 19]. As reported above, 4-methoxyphenylacetylene chromophore is ideal for generating the exciton coupling CD *Cotton* effects together with 4-methoxybenzoate group leading to the unambiguous determination of absolute configuration of chiral acetylene alcohols. The method was applied to chiral acetylene alcohols as follows.

Enantiopure 1-octyn-3-ol ((*S*)-(−)-**7**), which had been previously prepared by the *MαNP* acid method [13o], was converted to 4-methoxyphenylacetylene alcohol (+)-**8** by the *Sonogashira* reaction; a mixture of (−)-**7**, 4-iodoanisole, CuI, Et_3N, and $PdCl_2(PPh_3)_2$ was stirred overnight and then worked up yielding (+)-**8** in a good yield (Scheme 8). Alcohol (+)-**8** was then esterified with 4-methoxybenzoic acid giving benzoate (+)-**26**, the CD spectrum of which showed bisignate *Cotton* effects of positive exciton chirality as expected: $\lambda_{ext} = 266.2$ nm ($\Delta\varepsilon = +27.4\ mol^{-1}\ dm^3\ cm^{-1}$), 246.6 (−20.2), $A = +47.6$ (Fig. 22). From the data, the absolute configuration of benzoate (+)-**26** was determined as (*S*), confirming the previous absolute configurational assignment of alcohol (*S*)-(−)-**7** by the ^{1}H NMR anisotropy method using *MαNP* acid [13o].

As shown in Scheme 9, the same method was applied to 1-dodecyn-3-ol ((*R*)-(+)-**9**) [20], which was similarly converted to 4-methoxyphenylacetylene alcohol (−)-**10** in a good yield. Alcohol (−)-**10** was benzoylated giving 4-methoxybenzoate (−)-**27**, the CD spectrum of which showed exciton *Cotton* effects of negative chirality leading to the (*R*) absolute configuration: $\lambda_{ext} = 266.0$ nm ($\Delta\varepsilon = -27.9\ mol^{-1}\ dm^3\ cm^{-1}$), 246.2 (+21.0), $A = -48.9$ (Fig. 23). The (*R*) absolute



(a) 4-Iodoanisole, CuI, Et_3N, $PdCl_2(PPh_3)_2$, rt, 84%;
(b) 4-methoxybenzoic acid, *DCC*, *DMAP*, CH_2Cl_2, rt, 99%

Scheme 9

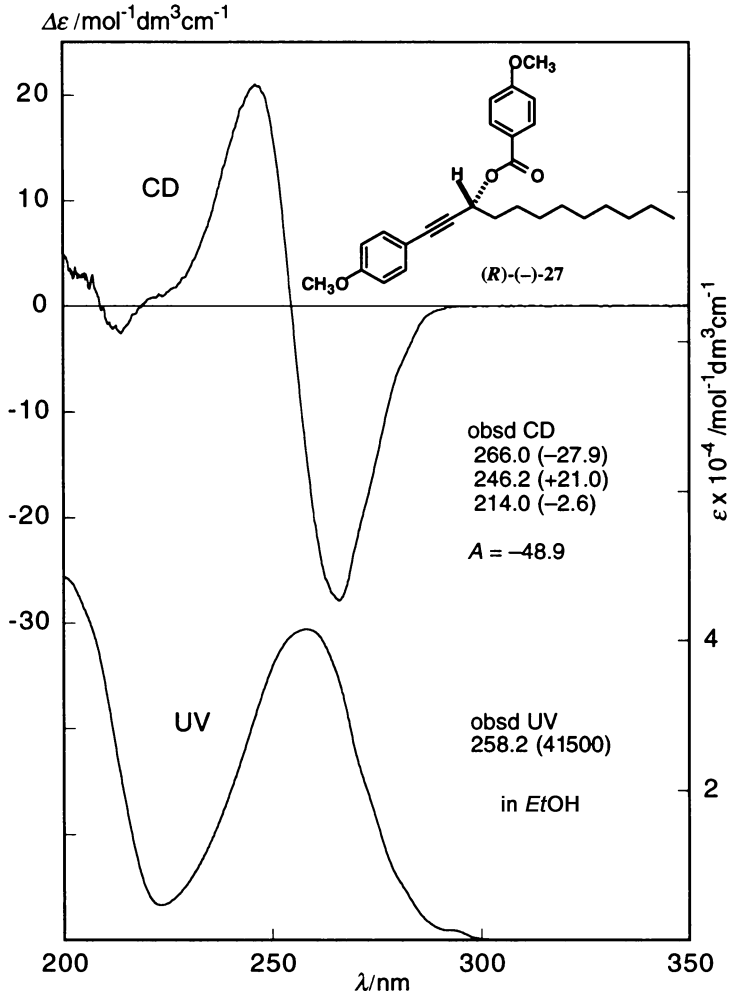


Fig. 23. CD and UV spectra of benzoate (*R*)-(−)-**27** in *Et*OH

configuration of benzoate (−)-**27** determined by the CD exciton chirality method thus agreed with the (*R*) absolute configuration of acetylene alcohol (+)-**9** assigned by the ^{1}H NMR anisotropy method using *MαNP* acid [20].

Conclusion

The absolute configurations of phenylacetylene alcohols were determined by observing intense bisignate CD *Cotton* effects due to the exciton coupling between phenylacetylene and benzoate chromophores. As an extension of the results, we developed a general methodology for determining the absolute configurations of chiral acetylene alcohols having the HC≡CCH(OH)-moiety by combination of the *Sonogashira* reaction and the CD exciton chirality method. The absolute configurations determined by the CD exciton chirality method agreed with those by the ^{1}H NMR anisotropy method using *MαNP* acid. Further applications of the *Sonogashira*/CD exciton chirality method to other acetylene alcohols are now in progress.

Experimental

IR spectra were obtained as neat, film on KBr, or KBr disks on a Jasco FT/IR-410 spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol JNM-LA400 (400 MHz) and/or a Jeol JNM-LA600 (600 MHz) spectrometer. ^{13}C NMR spectra were obtained on a Jeol JNM-LA400 (100 MHz) and/or a Jeol JNM-LA600 (150 MHz) spectrometer. All NMR data are reported in ppm (δ) downfield from *TMS*. Optical rotations $[\alpha]_D$ were measured on a Jasco DIP-1000 spectropolarimeter. Silica gel 60 F_{254} precoated plates on glass from Merck Ltd. were used for thinlayer chromatography (TLC). HPLC separation was performed using prepacked glass columns (22×300 mm, or 25×400 mm) of silica gel (particle size 5–10 μm) from Kusano Co., Ltd. The purities of the title compounds were shown to be $\geq$99% by ^{1}H NMR, TLC, HPLC, and/or elemental analyses, which matched the calculated values within experimental errors.

1-(4-Methoxyphenyl)-2,2-dibromoethylene (**12**, $C_9H_8Br_2O$)

To a mixture of 5.72 g P*Ph*$_3$ (21.8 mmol), 3.63 g CBr_4 (10.9 mmol) in 20 cm^3 of CH_2Cl_2 was added dropwise at room temperature 0.742 g of 4-methoxybenzaldehyde (5.45 mmol). After being stirred for 10 min at room temperature, the mixture was treated with aqueous $NaHCO_3$ solution and stirred for 10 min. The mixture was extracted with *Et*O*Ac*, and the organic layer was filtered with Celite, washed with brine, and evaporated under reduced pressure. The residue was subjected to a short column chromatography on silica gel (*n*-hexane/*Et*O*Ac* = 4/1) giving 1.78 g **12** (99%): colorless solid; mp 34°C; IR (KBr): $\bar{\nu} = 3285$, 2940, 2838, 1578, 1504, 1412, 1334, 1237, 1129 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.41 (s, 1H), 7.51 (d, $J = 8.7$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.3$, 87.3, 113.8, 127.8, 129.9, 136.3, 159.6 ppm.

4-(4-Methoxyphenyl)-3-butyn-2-ol (**4**, $C_{11}H_{12}O_2$)

To a solution of 1.00 g **12** (3.43 mmol) in 10 cm^3 of dried *THF* cooled at −78°C, was added a solution of *n*-BuLi (1.54 *M* hexane solution, 5.34 cm^3, 8.23 mmol) dropwise. After stirring for 15 min at −78°C, 1.00 g of acetaldehyde (22.7 mmol) was added, and the mixture was stirred at room temperature for 20 min. Aqueous NH_4Cl solution was added at 0°C, and the mixture was extracted with *Et*O*Ac*. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to a short column chromatography on silica gel (*n*-hexane/*Et*O*Ac* = 2/1) giving 0.475 g **4** (79%): colorless solid; mp 46°C; IR (KBr): $\bar{\nu} = 3365$, 2980, 2934, 2838, 1607, 1510, 1290, 1250, 1174, 1106, 1031, 833 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.54$ (d, $J = 6.3$ Hz, 3H), 2.04 (d, $J = 5.2$ Hz, 1H), 3.80 (s, 3H), 4.74 (qd, $J = 6.3$, 5.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.4$, 55.2, 58.9, 83.9, 89.6, 113.9, 114.6, 133.1, 159.6 ppm.

3-(3,4,5-Trimethoxyphenyl)propynal (**14**, $C_{12}H_{12}O_4$)

A mixture of 0.666 g of 3-(3,4,5-trimethoxyphenyl)propynol (**13**, 3.00 mmol) and 1.35 g of pyridinium dichlorochromate (*PDC*, 3.60 mmol) in 30 cm^3 CH_2Cl_2 was stirred at room temperature for 1 h. After addition of aqueous Na_2SO_3, the mixture was evaporated under reduced pressure. The residue was subjected to a short column chromatography on silica gel (*n*-hexane/*Et*O*Ac* = 2/1) giving 0.427 g **14** (65%): colorless crystals; mp 92°C; IR (KBr): $\bar{\nu} = 2981$, 2945, 2863, 2837, 2186, 1666, 1578, 1498, 1415, 1345, 1247, 1120, 1059, 1020, 996, 869, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.88$ (s, 6H), 3.90 (s, 3H), 6.86 (s, 2H), 9.40 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.2$, 61.0, 88.0, 95.7, 110.6, 113.9, 141.5, 153.2, 176.6 ppm.

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol (**5**, $C_{13}H_{16}O_4$)

To a solution of 0.220 g **14** (1.00 mmol) in 10 cm^3 of dried *THF* cooled at 0°C, was added a solution of *Me*MgBr (1.4 *M* in *THF*, 1.00 cm^3, 1.4 mmol) dropwise, and the mixture was stirred at room temperature for 1 h. After addition of aqueous saturated NH_4Cl, the mixture was extracted with *Et*OA*c*. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to a column chromatography on silica gel (*n*-hexane/*Et*OA*c* = 2/1) giving 0.225 g **5** (95%): colorless crystals; mp 74.5°C; IR (KBr): $\bar{\nu} = 3445$, 2981, 2936, 2840, 1579, 1505, 1452, 1411, 1236, 1129 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.56$ (d, $J = 6.6$ Hz, 3H), 2.31 (d, $J = 4.9$ Hz, 1H), 3.84 (s, 6H), 3.85 (s, 3H), 4.76 (qd, $J = 6.6$, 4.9 Hz, 1H), 6.66 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.3$, 56.0, 58.7, 60.9, 83.8, 90.0, 108.8, 117.5, 138.7, 152.9 ppm.

1-Phenyl-3-(3,4,5-trimethoxyphenyl)propynol (**6**, $C_{18}H_{18}O_4$)

To a solution of 0.050 g **14** (0.28 mmol) in 3 cm^3 of dried *THF* cooled at 0°C, was added a solution of *Ph*MgBr (1.0 *M* in *THF*, 0.5 cm^3, 0.5 mmol) dropwise, and the mixture was stirred at room temperature for 1 h. After addition of aqueous saturated NH_4Cl, the mixture was extracted with *Et*OA*c*. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to a column chromatography on silica gel (*n*-hexane/*Et*OA*c* = 2/1) giving 0.061 g **6** (84%): colorless oil; IR (neat): $\bar{\nu} = 3444$, 2940, 2838, 2190, 1579, 1504, 1452, 1412, 1237, 1128, 1001, 834, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (d, $J = 5.9$ Hz, 1H), 3.85 (s, 6H), 3.85 (s, 3H), 5.70 (d, $J = 5.9$ Hz, 1H), 6.71 (s, 2H), 7.34–7.46 (m, 3H), 7.60–7.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.1$, 61.0, 65.1, 86.6, 87.7, 108.9, 117.3, 126.7, 128.5, 128.7, 139.0, 140.6, 153.0 ppm.

*Enantioresolution of Racemic Phenylacetylene Alcohols **4–6** as CSDP Acid Esters*

A mixture of 0.340 g (±)-**4** (1.93 mmol), 1.00 g *CSDP* acid (2.32 mmol), 0.556 g *DCC* (2.70 mmol), and 0.047 g *DMAP* (0.39 mmol) in 10 cm^3 CH_2Cl_2 was stirred at room temperature overnight. After addition of 0.3 cm^3 of water, the mixture was stirred for 1 h, diluted with *Et*OA*c*, and filtered with Celite, which was washed with *Et*OA*c*. The organic layer was evaporated under reduced pressure, and the residue was subjected to a short column chromatography on silica gel (*n*-hexane/*Et*OA*c* = 3/1). The crude diastereomeric esters were separated by HPLC on silica gel (25 × 300 mm column, *n*-hexane/*Et*OA*c* = 3/1) giving 0.554 g of the first-eluted ester **15a** (49%) and 0.530 g of the second-eluted one **15b** (46%) (Table 1).

4-(4-Methoxyphenyl)-3-butyn-2-ol CSDP ester ((*S*)-(−)-**15a**, $C_{29}H_{29}Cl_2NO_6S$)

Amorphous solid; $[\alpha]_D^{28} = -99.8°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.22$, $CHCl_3$); IR (KBr): $\bar{\nu} = 2963$, 1728, 1686, 1606, 1510, 1337, 1292, 1247, 1169, 1142, 1091, 1022, 834, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (s, 3H), 1.21 (s, 3H), 1.30–1.41 (m, 2H), 1.65 (d, $J = 6.6$ Hz, 3H), 1.87–1.95 (m, 3H), 2.13 (br s, 1H), 2.47 (br d, $J = 12.7$ Hz, 1H), 3.37 (d, $J = 13.7$ Hz, 1H), 3.43 (d, $J = 13.7$ Hz, 1H), 3.80 (s, 3H), 4.07 (br dd, $J = 12.7$, 5.2 Hz, 1H), 5.84 (q, $J = 6.6$ Hz, 1H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.53 (s, 1H), 8.13 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 20.6, 21.5, 26.4, 33.1, 37.5, 44.7, 47.7, 48.4, 53.0, 55.2, 62.8, 65.7, 85.4, 85.4, 113.9, 114.0, 128.5, 131.1, 131.6, 133.4, 134.8, 134.8, 136.8, 159.9, 162.4, 165.2 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 254.0$ (33300), 206.8 (52000) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 264.8$ (−6.1), 244.4 (−5.5), 213.2 (+16.5) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(4-Methoxyphenyl)-3-butyn-2-ol CSDP ester ((*R*)-(−)-**15b**, $C_{29}H_{29}Cl_2NO_6S$)

Amorphous solid; $[\alpha]_D^{30} = -48.2°cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.10$, $CHCl_3$); IR (KBr): $\bar{\nu} = 2960$, 1730, 1686, 1607, 1510, 1337, 1296, 1248, 1170, 1142, 1061, 1025, 834, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (s, 3H), 1.20 (s, 3H), 1.31–1.36 (m, 2H), 1.68 (d, $J = 6.6$ Hz, 3H), 1.83–1.90 (m, 3H), 2.14 (br dd, $J = 12.6$, 7.8 Hz, 1H), 2.50 (br d, $J = 12.6$ Hz, 1H), 3.34 (d, $J = 13.8$ Hz, 1H), 3.39 (d, $J = 13.8$ Hz, 1H), 3.80 (s, 3H), 4.07 (br dd, $J = 5.9$, 5.9 Hz, 1H), 5.85 (q, $J = 6.6$ Hz, 1H), 6.83 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 9.0$ Hz, 2H), 7.51 (s, 1H), 8.15 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.9$, 20.7, 21.6, 26.4, 32.9, 37.6, 44.7, 47.7, 48.5, 52.8, 55.2, 62.8, 65.6, 85.2, 85.5, 113.8, 114.2, 128.2, 130.8, 131.8, 133.3, 134.7, 134.9, 136.8, 159.8, 162.3, 165.1 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 253.4$ (33400), 206.4 (52800) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 249.4$ (−12.6), 220.8 (+3.7), 215.6 (−2.3), 212.8 (−2.0), 204.0 (+19.7), 201.6 (+23.4) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(4-Methoxyphenyl)-3-butyn-2-ol ((*S*)-(−)-**4**, $C_{11}H_{12}O_2$)

A mixture of 0.292 g (*S*)-(−)-**15a** (0.494 mmol) and 0.500 g K_2CO_3 (excess) in 6 cm^3 *Me*OH was stirred at room temperature overnight. After filtration with Celite, the organic layer was evaporated under reduced pressure, and the residue was subjected to a short column chromatography on silica gel (*n*-hexane/*Et*OAc = 2/1). The crude alcohol was further purified by HPLC on silica gel (25 × 300 mm column, *n*-hexane/*Et*OAc = 4/1) giving 0.072 g (*S*)-(−)-**4** (83%): colorless oil; $[\alpha]_D^{26} = -29.6°cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.44$, $CHCl_3$); IR (neat): $\bar{\nu} = 3365$, 2980, 2934, 2838, 1607, 1510, 1290, 1250, 1174, 1106, 1031, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.54$ (d, $J = 6.3$ Hz, 3H), 2.04 (d, $J = 5.2$ Hz, 1H), 3.80 (s, 3H), 4.74 (qd, $J = 6.3$, 5.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.4$, 55.2, 58.9, 83.9, 89.6, 113.9, 114.6, 133.1, 159.6 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 252.0$ (23700), 202.4 (28500) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

*Enantioresolution of Racemic Acetylene Alcohols **5** by the CSDP Acid Method*

In a similar way, 0.150 g (±)-**5** were converted to *CSDP* esters, which were separated by HPLC on silica gel (25 × 300 mm column, *n*-hexane/*Et*OAc = 3/1) giving 0.179 g of the first-eluted ester **16a** (43%) and 0.168 g of the second-eluted one **16b** (41%) (Table 1).

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol CSDP ester ((*S*)-(−)-1**6a**, $C_{31}H_{33}Cl_2NO_8S$)

Amorphous solid; $[\alpha]_D^{32} = -93.7°cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.970$, $CHCl_3$); IR (KBr): $\bar{\nu} = 2941$, 1730, 1687, 1579, 1505, 1412, 1335, 1298, 1242, 1130, 1092, 910, 732, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (s, 3H), 1.22 (s, 3H), 1.31–1.44 (m, 2H), 1.67 (d, $J = 6.6$ Hz, 3H), 1.90–1.96 (m, 3H), 2.15 (br s, 1H), 2.46 (br d, $J = 12.7$ Hz, 1H), 3.38 (d, $J = 13.9$ Hz, 1H), 3.44 (d, $J = 13.9$ Hz, 1H), 4.07 (dd, $J = 12.7$, 7.6 Hz, 1H), 5.84 (q, $J = 6.6$ Hz, 1H), 6.70 (s, 2H), 7.54 (s, 1H), 8.14 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 20.7, 21.5, 26.4, 33.1, 37.6, 44.8, 47.7, 48.4, 53.0, 56.2, 60.9, 62.6, 65.7, 85.4, 85.8, 109.1, 117.0, 128.4, 131.1, 131.6, 134.9, 134.9, 136.9, 139.2, 153.0, 162.4, 165.2 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 256.6$ (23600), 216.6 (77200) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 246.2$ (−9.20), 221.6 (+35.0), 209.0 (−19.6) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol CSDP ester ((*R*)-(−)-**16b**, $C_{31}H_{33}Cl_2NO_8S$)

Colorless crystals; mp 157°C; $[\alpha]_D^{26} = -52.6°cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.05$, $CHCl_3$); IR (KBr): $\bar{\nu} = 2941$, 1731, 1686, 1578, 1505, 1335, 1298, 1241, 1129, 1091, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (s, 3H), 1.21 (s, 3H), 1.33–1.41 (m, 2H), 1.69 (d, $J = 6.6$ Hz, 3H), 1.87–1.92 (m, 3H), 2.15 (br dd, $J = 12.6$, 7.8 Hz, 1H), 2.51 (br d, $J = 12.6$ Hz, 1H), 3.37 (d, $J = 13.9$ Hz, 1H), 3.38 (d, $J = 13.9$ Hz, 1H), 3.85 (s, 6H), 3.85 (s, 3H), 4.07 (br s, 1H), 5.85 (q, $J = 6.6$ Hz, 1H), 6.70 (s, 2H),

7.52 (s, 1H), 8.16 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 20.8, 21.5, 26.4, 32.9, 37.7, 44.7, 47.7, 48.5, 52.9, 56.2, 60.9, 62.6, 65.7, 85.3, 85.9, 109.1, 117.1, 128.0, 130.9, 131.8, 134.8, 134.9, 137.0, 139.1, 153.0, 162.3, 165.1 ppm; UV (20% dioxane/*Et*OH): $\lambda_{max}(\varepsilon) = 256.2$ (24400), 217.0 (79100) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (20% dioxane/*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 250.2$ (−10.8), 222.6 (−29.9), 211.0 (+38.8) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol ((*S*)-(−)-**5**, $C_{13}H_{11}O$)

Similarly 0.165 g (*S*)-(−)-**16a** were treated with K_2CO_3 in *Me*OH yielding 0.050 g (*S*)-(−)-**5** (84%): colorless oil; $[\alpha]_D^{25} = -21.0°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.00$, $CHCl_3$); IR (neat): $\bar{\nu} = 2981$, 2945, 2863, 2837, 2186, 1666, 1578, 1498, 1415, 1345, 1247, 1120, 1059, 1020, 996, 869, 831 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.88$ (s, 6H), 3.90 (s, 3H), 6.86 (s, 2H), 9.40 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.2$, 61.0, 88.0, 95.7, 110.6, 113.9, 141.5, 153.2, 176.6 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 265.2$ (15700), 215.8 (40500) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

*Enantioresolution of Racemic Acetylene Alcohols **6** by the CSDP Acid Method*

Similarly 0.200 g (±)-**6** were converted to *CSDP* esters, which were separated by HPLC on silica gel (25 × 300 mm column, *n*-hexane/*Et*OAc = 2/1) giving 0.200 g of the first-eluted ester **17a** (42%) and 0.209 g of the second-eluted one **17b** (44%) (Table 1).

1-Phenyl-3-(3,4,5-trimethoxyphenyl)propynol CSDP ester ((*S*)-(−)-**17a**, $C_{36}H_{35}Cl_2NO_8S$)

Amorphous solid; $[\alpha]_D^{31} = -53.1°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.962$, $CHCl_3$); IR (KBr): $\bar{\nu} = 2961$, 1731, 1687, 1579, 1504, 1336, 1298, 1239, 1130, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (s, 3H), 1.17 (s, 3H), 1.30–1.34 (m, 2H), 1.85–1.91 (m, 3H), 2.11 (br dd, $J = 13.5$, 7.6 Hz, 1H), 2.48 (br d, 13.5 Hz, 1H), 3.31 (d, $J = 13.8$ Hz, 1H), 3.40 (d, $J = 13.8$ Hz, 1H), 3.85 (s, 6H), 3.85 (br s, 1H), 3.85 (s, 3H), 6.73 (s, 2H), 6.80 (s, 1H), 7.35–7.47 (m, 3H), 7.52 (s, 1H), 7.65 (dd, $J = 7.3$, 1.3 Hz, 2H), 8.15 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 20.7, 26.4, 32.9, 37.6, 44.7, 47.7, 48.4, 53.0, 56.2, 60.9, 65.5, 67.7, 83.8, 88.0, 109.2, 116.8, 127.4, 128.0, 128.1, 128.7, 129.1, 131.1, 131.9, 134.9, 136.2, 137.1, 139.3, 153.0, 162.5, 165.0 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 256.8$ (21300), 216.8 (70500) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 255.0$ (−5.6), 224.2 (−3.2), 208.0 (+10.8) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-Phenyl-3-(3,4,5-trimethoxyphenyl)propynol CSDP ester ((*R*)-(−)-**17b**, $C_{36}H_{35}Cl_2NO_8S$)

Amorphous solid; $[\alpha]_D^{31} = -58.9°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.822$, $CHCl_3$); IR (KBr): $\bar{\nu} = 2961$, 1731, 1686, 1579, 1504, 1336, 1299, 1240, 1130, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (s, 3H), 1.22 (s, 3H), 1.31–1.36 (m, 2H), 1.85–1.96 (m, 3H), 2.11 (br dd, $J = 13.2$, 7.6 Hz, 1H), 2.48 (br d, $J =$ 13.2 Hz, 1H), 3.34 (d, $J = 13.8$ Hz, 1H), 3.38 (d, $J = 13.8$ Hz, 1H), 3.85 (s, 6H), 3.85 (s, 3H), 3.93 (br s, 1H), 6.73 (s, 2H), 6.82 (s, 1H), 7.37–7.47 (m, 3H), 7.52 (s, 1H), 7.65 (dd, $J = 8.1$, 1.4 Hz, 2H), 8.10 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.0$, 20.8, 26.4, 32.9, 37.7, 44.7, 47.7, 48.5, 52.9, 56.2, 61.0, 65.6, 67.7, 84.0, 87.8, 109.2, 117.0, 128.0, 128.1, 128.8, 129.2, 130.9, 131.9, 134.9, 134.9, 136.3, 137.0, 139.3, 153.0, 162.4, 165.0 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 256.8$ (17000), 216.8 (54600) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 255.0$ (−7.2), 224.2 (−4.1), 208.0 (+13.9) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-Phenyl-3-(3,4,5-trimethoxyphenyl)propynol ((*S*)-(+)-**6**, $C_{18}H_{18}O_4$)

Similarly 0.502 g (*S*)-(−)-**17a** were treated with K_2CO_3 in *Me*OH yielding 0.182 g (*S*)-(−)-**5** (87%): colorless solid; $[\alpha]_D^{33} = +2.8°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.29$, $CHCl_3$); IR (KBr): $\bar{\nu} = 3444$, 2940,

2838, 2190, 1579, 1504, 1452, 1412, 1237, 1128, 1001, 834, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (d, $J = 5.9$ Hz, 1H), 3.85 (s, 6H), 3.85 (s, 3H), 5.70 (d, $J = 5.9$ Hz, 1H), 6.71 (s, 2H), 7.34–7.46 (m, 3H), 7.60–7.64 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 56.1$, 61.0, 65.1, 86.6, 87.7, 108.9, 117.3, 126.7, 128.5, 128.7, 139.0, 140.6, 153.0 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 262.6$ (20200), 216.8 (42000) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 296.4$ (−0.5), 226.2 (−1.8) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(4-Methoxyphenyl)-3-butyn-2-ol MαNP ester ((*R*,*S*)-(+)-**18**, $C_{25}H_{24}O_4$)

A mixture of 0.020 g (−)-**4** (0.11 mmol), 0.036 g (*R*)-*MαNP* acid (0.16 mmol), 0.046 g *DCC* (0.22 mmol), 0.014 g *DMAP* (0.11 mmol), and 0.005 g of 10-camphorsulfonic acid (*CSA*, 0.02 mmol) in 1 cm^3 CH_2Cl_2 was stirred at room temperature overnight. After addition of 0.1 cm^3 of water, the mixture was stirred for 1 h, diluted with *Et*OAc, and filtered with Celite, which was washed with *Et*OAc. The organic layer was evaporated under reduced pressure, and the residue was purified by HPLC on silica gel (*n*-hexane/*Et*OAc = 3/1) giving 0.037 g (*R*,*S*)-(+)-**18** (86%): colorless syrup; $[\alpha]_D^{25} = +15.9°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.822$, $CHCl_3$); IR (neat): $\bar{\nu} = 3051$, 2989, 2937, 2835, 2229, 1738, 1606, 1510, 1291, 1250, 1174, 1135, 1107, 1025, 834, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$ (d, $J = 6.8$ Hz, 3H), 2.03 (s, 3H), 3.11 (s, 3H), 3.80 (s, 3H), 5.71 (q, $J = 6.8$ Hz, 1H), 6.81 (d, $J = 8.9$ Hz, 2H), 7.30 (d, $J = 8.9$ Hz, 2H), 7.40–7.70 (m, 3H), 7.62 (dd, $J = 7.3$, 1.0 Hz, 1H), 7.83 (d, $J = 7.8$ Hz, 1H), 7.84 (d, $J = 9.5$ Hz, 1H), 8.42 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.0$, 21.7, 51.0, 55.3, 61.9, 81.6, 84.8, 85.6, 113.8, 114.3, 124.6, 125.3, 125.6, 125.8, 126.4, 128.6, 129.5, 131.3, 133.3, 134.1, 134.8, 159.8, 173.1 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 292.2$ (6400), 281.2 (10200), 256.4 (26800), 224.2 (75000), 207.6 (48400) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 291.0$ (+4.0), 281.0 (+6.6), 271.2 (+5.7), 256.0 (−1.8), 228.2 (−3.2), 214.0 (+11.5), 208.8 (+12.3) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(4-Methoxyphenyl)-3-butyn-2-ol MαNP ester ((*S*,*S*)-(−)-**18**, $C_{25}H_{24}O_4$)

Similarly 0.017 g (−)-**4** were esterified with 0.032 g (*S*)-*MαNP* acid yielding 0.037 g of (*S*,*S*)-(−)-**18** (97%): colorless syrup; $[\alpha]_D^{26} = -31.5°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.42$, $CHCl_3$); IR (neat): $\bar{\nu} = 3053$, 2987, 2936, 2836, 1734, 1606, 1510, 1250, 1134, 1107, 1026, 834, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.46$ (d, $J = 6.8$ Hz, 3H), 2.01 (s, 3H), 3.15 (s, 3H), 3.80 (s, 3H), 5.71 (q, $J = 6.8$ Hz, 1H), 6.78 (d, $J = 9.0$ Hz, 2H), 7.15 (d, $J = 9.0$ Hz, 2H), 7.39–7.47 (m, 3H), 7.64 (dd, $J = 7.1$, 1.0 Hz, 1H), 7.81–7.86 (m, 2H), 8.39 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.1$, 22.1, 51.2, 55.2, 62.0, 81.8, 84.7, 85.4, 113.7, 114.3, 124.7, 125.2, 125.6, 125.6, 126.3, 128.7, 129.5, 131.2, 133.2, 134.1, 135.1, 159.7, 173.0 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 292.4$ (6400), 281.2 (9900), 256.2 (26200), 224.2 (74600), 207.2 (48200) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 281.8$ (+6.3), 256.6 (−8.2), 226.0 (+6.2), 215.6 (−7.7), 204.4 (+9.1) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol MαNP ester ((*R*,*S*)-(+)-**19**, $C_{27}H_{28}O_6$)

Similarly 0.014 g (−)-**5** were esterified with 0.019 g (*R*)-*MαNP* acid yielding 0.030 g (*R*,*S*)-(+)-**19** (99%): colorless crystals; mp 159°C; $[\alpha]_D^{34} = +9.5°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.41$, $CHCl_3$); IR (KBr): $\bar{\nu} = 2994$, 2939, 2831, 1740, 1578, 1505, 1452, 1412, 1237, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.28$ (d, $J = 6.8$ Hz, 3H), 2.04 (s, 3H), 3.10 (s, 3H), 3.82 (s, 6H), 3.85 (s, 3H), 5.71 (q, $J = 6.8$ Hz, 1H), 6.60 (s, 2H), 7.40–7.48 (m, 3H), 7.63 (dd, $J = 7.3$, 1.0 Hz, 1H), 7.83–7.87 (m, 2H), 8.41 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.9$, 21.7, 51.0, 56.1, 60.9, 61.7, 81.6, 84.8, 85.9, 109.1, 117.2, 124.6, 125.2, 125.6, 125.8, 126.4, 128.6, 129.5, 131.3, 134.0, 134.7, 139.0, 152.9, 173.1 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 262.6$ (17900), 220.6 (77000) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) =$ 280.8 (+4.5), 257.0 (−1.1), 219.6 (+7.6) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol MαNP ester ((*S*,*S*)-(−)-**19**, $C_{27}H_{28}O_6$)

Similarly 0.015 g (−)-**5** were esterified with 0.020 g (*S*)-*MαNP* acid yielding 0.030 g (*S*,*S*)-(−)-**19** (99%): colorless syrup; $[\alpha]_D^{35} = -34.4°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.47$, $CHCl_3$); IR (neat): $\bar{\nu} = 2989$, 2939, 2832, 1738, 1578, 1505, 1412, 1237, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.48$ (d, $J = 6.8$ Hz, 3H), 2.02 (s, 3H), 3.14 (s, 3H), 3.82 (s, 6H), 3.84 (s, 3H), 5.71 (q, $J = 6.8$ Hz, 1H), 6.50 (s, 2H), 7.37–7.42 (m, 2H), 7.46 (dd, $J = 7.3$, 8.1 Hz, 1H), 7.65 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.80–7.85 (m, 2H), 8.38 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.0$, 22.1, 51.2, 56.1, 60.9, 61.9, 81.7, 84.8, 85.7, 109.0, 117.2, 124.7, 125.2, 125.5, 125.6, 126.3, 128.6, 129.5, 131.2, 134.1, 135.1, 138.9, 152.8, 173.1 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 262.2$ (17700), 220.0 (76300) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 282.0$ (+5.1), 257.0 (−5.2), 225.8 (−14.8), 214.4 (+9.1), 204.0 (−4.0) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-Phenyl-3-(3,4,5-trimethoxyphenyl)propynol MαNP ester ((*R*,*S*)-(+)-**20**)

Similarly 0.038 g (+)-**6** were esterified with 0.044 g (*R*)-*MαNP* acid yielding 0.058 g (*R*,*S*)-(+)-**20** (89%): colorless syrup; $[\alpha]_D^{35} = +45.6°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.16$, $CHCl_3$); IR (neat): $\bar{\nu} = 3007$, 2940, 2832, 2225, 1741, 1578, 1504, 1454, 1412, 1236, 1130, 781, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.06$ (s, 3H), 3.12 (s, 3H), 3.82 (s, 6H), 3.85 (s, 3H), 6.64 (s, 2H), 6.69 (s, 1H), 7.00 (d, $J = 7.6$ Hz, 2H), 7.08 (dd, $J = 7.6$, 7.5 Hz, 2H), 7.17 (t, $J = 7.5$ Hz, 1H), 7.33 (ddd, $J = 8.5$, 6.8, 1.5 Hz, 1H), 7.38–7.45 (m, 2H), 7.60 (d, $J = 7.1$ Hz, 1H), 7.82 (d, $J = 8.3$ Hz, 1H), 7.83 (d, $J = 8.0$ Hz, 1H), 8.35 (d, $J = 8.5$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.6$, 51.0, 56.3, 60.9, 66.6, 81.7, 84.0, 87.2, 109.1, 117.0, 124.6, 125.1, 125.6, 125.9, 126.5, 126.9, 128.2, 128.4, 128.5, 129.5, 131.3, 134.0, 134.5, 136.2, 139.2, 152.9, 172.9 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 266.6$ (20300), 220.6 (80900) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 282.6$ (+3.6), 263.8 (−2.7), 222.6 (+36.0) nm ($mol^{-1}\,dm^3\,cm^{-1}$); HRMS (EI): m/z = calcd for $C_{32}H_{30}O_6$ $[M]^+$ 510.2042, found 510.2059.

1-Phenyl-3-(3,4,5-trimethoxyphenyl)propynol MαNP ester ((*S*,*S*)-(−)-**20**, $C_{32}H_{30}O_6$)

Similarly 0.044 g (+)-**6** were esterified with 0.050 g (*S*)-*MαNP* acid yielding 0.064 g (*S*,*S*)-(−)-**20** (86%): colorless crystals; mp 126°C; $[\alpha]_D^{35} = -21.9°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.28$, $CHCl_3$); IR (KBr): $\bar{\nu} = 3001$, 2939, 2832, 2229, 1737, 1578, 1505, 1455, 1412, 1236, 1129, 781, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.00$ (s, 3H), 3.13 (s, 3H), 3.82 (s, 6H), 3.85 (s, 3H), 6.51 (s, 2H), 6.72 (s, 1H), 7.25–7.35 (m, 5H), 7.35–7.45 (m, 3H), 7.60 (d, $J = 7.3$ Hz, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 7.81 (d, $J = 8.1$ Hz, 1H), 8.30 (d, $J = 8.5$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.0$, 51.2, 56.1, 60.9, 66.9, 81.8, 83.8, 87.3, 109.1, 117.0, 124.6, 125.1, 125.5, 125.6, 126.3, 127.6, 128.5, 128.5, 128.8, 129.4, 131.1, 134.0, 134.9, 136.4, 139.1, 152.8, 172.9 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 266.6$ (21900), 220.2 (87000) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 283.2$ (+3.6), 263.8 (−6.8), 227.0 (−15.8), 214.2 (+13.1) nm ($mol^{-1}\,dm^3\,cm^{-1}$); HRMS (EI): m/z = calcd for $C_{32}H_{30}O_6$ $[M]^+$ 510.2042, found 510.2044.

1-(4-Methoxyphenyl)-5-methyl-1-hexyn-3-ol 4-methoxybenzoate ((*S*)-(+)-**21**)

A mixture of 0.029 g (−)-**3** (0.13 mmol), 0.022 g of 4-methoxybenzoic acid (0.15 mmol), 0.033 g *DCC* (0.16 mmol), and 0.003 g *DMAP* (0.03 mmol) in 1 cm^3 CH_2Cl_2 was stirred at room temperature overnight. After addition of 0.1 cm^3 of water, the mixture was stirred for 1 h, diluted with *Et*O*Ac*, and filtered with Celite, which was washed with *Et*O*Ac*. The organic layer was evaporated under reduced pressure, and the residue was purified by HPLC on silica gel (*n*-hexane/*Et*O*Ac* = 4/1) giving 0.046 g (*S*)-(+)-**21** (98%): colorless syrup; $[\alpha]_D^{17} = +25.3°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.78$, $CHCl_3$); IR (neat): $\bar{\nu} = 3007$, 2957, 2933, 2871, 2839, 2225, 1714, 1606, 1581, 1510, 1466, 1440, 1420, 1366, 1318,

1254, 1168, 1097, 1032, 934, 833, 769, 698, 615, 575, 537, 518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (d, $J = 6.1$ Hz, 3H), 1.01 (d, $J = 6.1$ Hz, 3H), 1.80–1.92 (m, 2H), 1.96 (m, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 5.87 (t, $J = 6.8$ Hz, 1H), 6.82 (dt, $J = 9.0$, 2.7 Hz, 2H), 6.93 (dt, $J = 9.0$, 2.7 Hz, 2H), 7.38 (dt, $J = 9.0$, 2.7 Hz, 2H), 8.05 (dt, $J = 9.0$, 2.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.5$, 22.6, 24.9, 44.0, 55.3, 55.4, 63.7, 85.1, 85.7, 113.6, 113.8, 114.5, 122.5, 131.8, 133.4, 159.7, 163.4, 165.4 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 258.2$ (42800) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 266.0$ (+30.9), 246.4 (−22.7), 213.2 (+2.8) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(4-Methoxyphenyl)-3-butyn-2-ol 4-methoxybenzoate ((*S*)-(+)-**22**, $C_{19}H_{18}O_4$)

Similarly 0.018 g (−)-**4** were esterified with 0.022 g of 4-methoxybenzoic acid yielding 0.030 g (*S*)-(+)-**22** (93%): colorless syrup; $[\alpha]_D^{24} = +34.2°cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.49$, $CHCl_3$); IR (neat): $\bar{\nu} = 2935$, 2839, 1715, 1606, 1510, 1254, 1169, 1096, 1029, 833, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.69$ (d, $J = 6.6$ Hz, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 5.91 (q, $J = 6.6$ Hz, 1H), 6.82 (d, $J = 9.0$ Hz, 2H), 6.92 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 9.0$ Hz, 2H), 8.05 (d, $J = 9.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7$, 55.2, 55.4, 61.2, 84.5, 86.4, 113.5, 113.8, 114.4, 122.5, 131.8, 133.4, 159.7, 163.4, 165.3 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 258.8$ (40900) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 266.0$ (+26.3), 245.8 (−18.5), 214.8 (+2.6) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol 4-methoxybenzoate ((*S*)-(+)-**23**, $C_{22}H_{22}O_6$)

Similarly 0.018 g (−)-**5** were esterified with 0.017 g of 4-methoxybenzoic acid yielding 0.024 g (*S*)-(+)-**23** (87%): colorless syrup; $[\alpha]_D^{31} = +27.3°cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.20$, $CHCl_3$); IR (neat): $\bar{\nu} = 2939$, 2839, 1715, 1606, 1579, 1506, 1255, 1168, 1129, 1093, 1028, 769, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.70$ (d, $J = 6.8$ Hz, 3H), 3.84 (s, 6H), 3.87 (s, 3H), 5.90 (q, $J = 6.8$ Hz, 1H), 6.69 (s, 2H), 6.93 (d, $J = 9.0$ Hz, 2H), 8.06 (d, $J = 9.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.6$, 55.4, 56.1, 60.9, 61.0, 84.5, 86.8, 109.1, 113.6, 117.3, 122.3, 131.8, 139.0, 153.0, 163.5, 165.2 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 260.6$ (35700), 214.4 (52100) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 268.0$ (+22.0), 248.0 (−10.8), 224.8 (−2.7), 207.6 (−8.1) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

4-(3,4,5-Trimethoxyphenyl)-3-butyn-2-ol 3,4,5-trimethoxybenzoate ((*S*)-(+)-**24**, $C_{23}H_{26}O_8$)

Similarly 0.014 g (−)-**5** were esterified with 0.018 g of 3,4,5-trimethoxybenzoic acid yielding 0.025 g (*S*)-(+)-**24** (96%): colorless syrup; $[\alpha]_D^{35} = +16.4°cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.08$, $CHCl_3$); IR (neat): $\bar{\nu} = 2940$, 2840, 1716, 1579, 1505, 1458, 1415, 1344, 1327, 1223, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.73$ (d, $J = 6.6$ Hz, 3H), 3.85 (s, 6H), 3.85 (s, 3H), 3.91 (s, 3H), 3.93 (s, 6H), 5.92 (q, $J = 6.6$ Hz, 1H), 6.70 (s, 2H), 7.35 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.6$, 56.1, 56.3, 60.9, 60.9, 61.5, 84.8, 86.5, 107.0, 109.1, 117.2, 124.9, 139.1, 142.4, 152.9, 153.0, 165.2 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 265.2$ (25300), 215.8 (67500) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 273.0$ (+12.0), 252.0 (−6.5), 222.2 (+5.7), 209.6 (−12.4) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-Phenyl-3-(3,4,5-trimethoxyphenyl)propynol 4-methoxybenzoate ((*S*)-(+)-**25**, $C_{26}H_{24}O_6$)

Similarly 0.029 g (+)-**6** were esterified with 0.022 g of 4-methoxybenzoic acid yielding 0.045 g (*S*)-(+)-**25** (99%): colorless syrup; $[\alpha]_D^{34} = +28.6°cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.932$, $CHCl_3$); IR (neat): $\bar{\nu} = 2939$, 2839, 1715, 1606, 1579, 1506, 1255, 1168, 1129, 1093, 1028, 769, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.84$ (s, 6H), 3.84 (s, 3H), 6.72 (s, 2H), 6.92 (d, $J = 9.0$ Hz, 2H), 6.92 (s, 1H), 7.36–7.46 (m, 3H), 7.68 (d, $J = 7.8$ Hz, 2H), 8.07 (d, $J = 9.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.4$, 56.1, 60.9, 66.2, 84.9, 87.0, 109.1, 113.6, 117.1, 122.1, 127.6, 128.7, 128.8, 132.0, 137.4, 139.1, 153.0, 163.6, 165.1 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 261.0$ (34500),

212.6 (50500) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 273.4$ (+16.2), 250.4 (−13.0), 224.0 (−5.1), 212.6 (+3.3) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-(4-Methoxyphenyl)-1-octyn-3-ol ((*S*)-(+)-**8**, $C_{15}H_{20}O_2$)

A mixture of 0.040 g of enantiopure 1-octyn-3-ol (*S*)-(−)-**7** [13o] ($[\alpha]_D^{27} = -10.4°\,cm^3\,g^{-1}\,dm^{-1}$ (neat, $\rho = 0.864$), $[\alpha]_D^{27} = -6.37°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.82$, $CHCl_3$), 0.32 mmol), 0.148 g of 4-iodoanisole (0.63 mmol), 0.0012 g CuI (0.006 mmol), and 0.5 cm^3 Et_3N was degassed by freezing in a liquid N_2 bath under vacuum, and then 0.009 g $PdCl_2(PPh_2)_2$ (0.013 mmol) were added at room temperature. The reaction mixture was vigorously stirred overnight. After evaporation of the solvent under reduced pressure, *Et*O*Ac* was added, and the mixture was filtered with Celite, which was washed with *Et*O*Ac*. The organic layer was evaporated under reduced pressure, and the residue was purified by HPLC on silica gel (*n*-hexane/*Et*O*Ac* = 6/1) giving 0.057 g (*S*)-(+)-**8** (78%): colorless oil; $[\alpha]_D^{25} = +6.7°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.25$, $CHCl_3$); IR (neat): $\bar{\nu} = 3364$, 2933, 2859, 2226, 1607, 1570, 1509, 1465, 1290, 1249, 1173, 1107, 1033, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.0$ Hz, 3H), 1.32–1.36 (m, 4H), 1.52 (m, 2H), 1.75–1.82 (m, 2H), 1.85 (d, $J = 5.5$ Hz, 1H), 3.81 (s, 3H), 4.87 (td, $J = 6.5$, 5.5 Hz, 1H), 6.33 (d, $J = 10.0$ Hz, 2H), 7.36 (d, $J = 10.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.01$, 22.57, 24.91, 31.48, 37.95, 55.27, 63.09, 84.71, 88.81, 113.89, 114.75, 133.12, 159.62 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 294.6$ (1300), 283.2 (2000), 252.2 (23800), 202.6 (26800) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 251.6$ (+0.5) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-(4-Methoxyphenyl)-1-octyn-3-ol 4-methoxybenzoate ((*S*)-(+)-**26**, $C_{23}H_{26}O_4$)

Similarly 0.037 g (+)-**8** were esterified with 0.048 g of 4-methoxybenzoic acid yielding 0.053 g (*S*)-(+)-**26** (99%): colorless syrup; $[\alpha]_D^{24} = +28.8°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.920$, $CHCl_3$); IR (neat): $\bar{\nu} = 2933$, 2860, 2230, 1714, 1606, 1510, 1464, 1252, 1168, 1096, 1031, 832, 770, 418 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (t, $J = 7.1$ Hz, 3H), 1.38 (m, 4H), 1.58 (m, 2H), 1.94 (dddd, $J = 13.2$, 8.3, 7.3, 6.6 Hz, 1H), 1.98 (dddd, $J = 13.2$, 8.3, 7.3, 6.6 Hz, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 5.81 (t, $J = 6.6$ Hz, 1H), 6.82 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 8.9$ Hz, 2H), 8.05 (d, $J = 9.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.98$, 22.50, 24.84, 31.36, 35.12, 55.26, 55.43, 64.92, 85.09, 85.56, 113.57, 113.81, 114.55, 122.55, 131.83, 133.37, 159.72, 163.43, 165.39 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 258.6$ (39800) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) =$ 266.2 (+27.4), 246.6 (−20.2) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-(4-Methoxyphenyl)-1-dodecyn-3-ol ((*R*)-(−)-**10**, $C_{19}H_{28}O_2$)

Similarly 0.056 g of enantiopure 1-dodecyn-3-ol (*R*)-(+)-**9** [20] ($[\alpha]_D^{21} = +3.0°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.13$, $CHCl_3$)) were converted to 0.075 g (*R*)-(−)-**10** (84%) by the *Sonogashira* reaction: colorless oil; $[\alpha]_D^{23} = -8.4°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.92$, $CHCl_3$); IR (neat): $\bar{\nu} = 3344$, 2926, 2854, 1607, 1509, 1466, 1290, 1249, 1173, 1035, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$ (t, $J = 6.8$ Hz, 3H), 1.27–1.42 (m, 12H), 1.45–1.53 (m, 2H), 1.72–1.82 (m, 2H), 1.86 (d, $J = 5.9$ Hz, 1H), 3.81 (s, 3H), 4.58 (td, 6.2, 5.9 Hz, 1H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.36 (d, $J = 8.8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 22.7, 25.2, 29.3, 29.3, 29.5, 29.5, 31.9, 38.0, 55.3, 63.1, 84.7, 88.8, 113.9, 114.7, 133.1, 159.6 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 294.6$ (1300), 283.0 (2000), 252.2 (24400), 202.4 (29100) nm ($mol^{-1}\,dm^3\,cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 250.6$ (−0.5) nm ($mol^{-1}\,dm^3\,cm^{-1}$).

1-(4-Methoxyphenyl)-1-dodecyn-3-ol 4-methoxybenzoate ((*R*)-(−)-**27**, $C_{27}H_{34}O_4$)

Similarly 0.034 g (−)-**10** were esterified with 0.036 g of 4-methoxybenzoic acid yielding 0.051 g (*R*)-(−)-**27** (99%): colorless syrup; $[\alpha]_D^{22} = -24.0°\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 1.01$, $CHCl_3$); IR (neat): $\bar{\nu} = 2927$,

2855, 2229, 1715, 1606, 1510, 1254, 1168, 1097, 1032, 832, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.0$ Hz, 3H), 1.25–1.40 (m, 12H), 1.52–1.60 (m, 2H), 1.96 (m, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 5.81 (t, $J = 6.6$ Hz, 1H), 6.82 (d, $J = 9.0$ Hz, 2H), 6.93 (d, $J = 9.0$ Hz, 2H), 7.39 (d, $J = 8.9$ Hz, 2H), 8.05 (d, $J = 8.9$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 22.6, 25.1, 29.2, 29.3, 29.5, 29.5, 31.9, 35.1, 55.2, 55.4, 64.9, 85.1, 85.6, 113.5, 113.8, 114.5, 122.5, 131.8, 133.4, 159.7, 163.4, 165.4 ppm; UV (*Et*OH): $\lambda_{max}(\varepsilon) = 258.2$ (41500) nm ($mol^{-1}\ dm^3\ cm^{-1}$); CD (*Et*OH): $\lambda_{ext}(\Delta\varepsilon) = 266.0$ (−27.9), 246.2 (+21.0), 214.0 (−2.6) nm ($mol^{-1}\ dm^3\ cm^{-1}$).

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[20] Preparation of enantiopure alcohol (*R*)-(+)-**9** and determination of its absolute configuration by the *MαNP* acid method will be published elsewhere