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The Chiral Amino Alcohol, *cis*-2-Amino-1-acenaphthenol: Synthesis, Resolution, and Application to the Diastereoselective [2,3]-Wittig Rearrangement

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Abstract: The chiral amino alcohol, *cis*-2-amino-1-acenaphthenol, was synthesized, and resolved by a simple procedure. This new chiral amino alcohol was converted into an oxazoline derivative and applied as a chiral auxiliary to the diastereoselective [2,3]-Wittig rearrangement.

Introduction:

The development and application of artificial chiral auxiliaries derived from non-natural materials have attracted considerable attention,[1] aided by the progress in the techniques and knowledge concerning the optical resolution of racemates.[2] In contrast to the case of natural products and their derivatives, there are two favorable characteristics in using non-natural chiral sources: 1) Both enantiomers are readily available and can each be used in asymmetric reactions. 2) The structure can be designed in contrast to natural chiral compounds, which can have structural characteristics unsuitable for an asymmetric reaction. In this paper, we report the synthesis and resolution of the amino alcohol, *cis*-2-amino-1-acenaphthenol, and its application to the diastereoselective [2,3]-Wittig sigmatropic rearrangement.

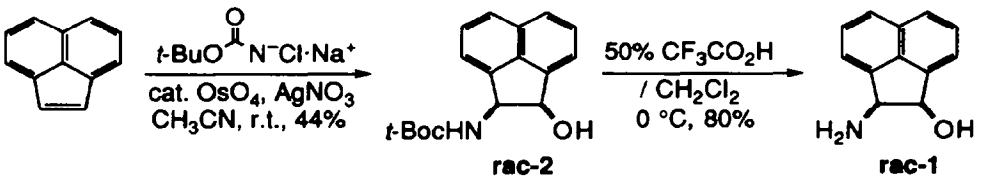
Results and Discussion:

Chiral vicinal amino alcohols have played a significant role in asymmetric syntheses as precursors of chiral auxiliaries[3] or chiral ligands for numerous types of metallic reagents.[4] Most of them, except for camphor derivatives,[5] have free rotation around the single bond between the vicinal stereogenic carbons bearing the hydroxyl and amino groups. On the other hand, we have already reported that *erythro*-2-amino-1,2-diphenylethanol[6] can be successfully resolved into its enantiomers. However, since the amino alcohol has the possibility of free-rotation as mentioned above, this sometimes makes the prediction of the conformation and the interactions with substrates in an asymmetric induction process unreliable. Therefore, we designed a vicinal *cis*-

amino alcohol with a rigid skeleton, in which the orientation of amino and hydroxyl groups is fixed by combination of the two phenyl groups of *erythro*-2-amino-1,2-diphenylethanol into a naphthalene ring. On the basis of this idea, we selected *cis*-2-amino-1-acenaphthenol **1** as a new chiral auxiliary.

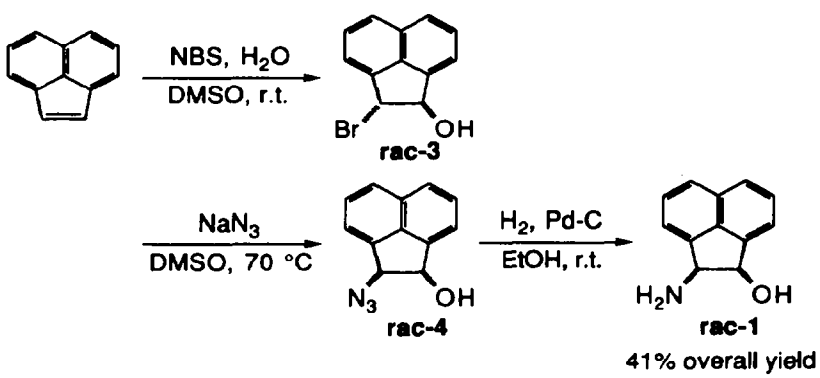
The synthesis of racemic *cis*-2-amino-1-acenaphthenol has been reported only on a small scale.[7] A new route for the synthesis of racemic *cis*-2-amino-1-acenaphthenol **rac-1** was achieved by using the Sharpless *cis*-hydroxyamination,[8] which gave **rac-1** via only two steps starting from acenaphthylene: Treatment of acenaphthylene with a catalytic amount of osmium tetroxide, 1.5 eq. *tert*-butyl *N*-chloro-*N*-sodiocarbamate, and 3.0 eq. silver nitrate in acetonitrile gave racemic *cis*-Boc-amino alcohol **rac-2** in 44% yield (Scheme 1). No *trans*-product was detected. Deprotection of *N*-Boc group of **rac-2** with 50% trifluoroacetic acid in dichloromethane at 0 °C afforded **rac-1** in 80% yield. This method is very straightforward and allows a preparation of 0.5-1 g of **rac-1** in each run. Since this amino alcohol was sensitive to air, the isolation and purification were carried out as its cinnamic acid salt.

Scheme 1



Although this route provided **rac-1**, the expense and toxicity of osmium tetroxide were considered to prohibit a large scale operation. An alternative method for a large scale preparation of **rac-1** was developed via hydroxyhalogenation followed by azidation and reduction (Scheme 2):[9] Acenaphthylene was converted to racemic *trans*-bromohydrin **rac-3** by the reaction with *N*-bromosuccinimide and water in dimethylsulfoxide. *trans*-Bromohydrin **rac-3** was converted to racemic *cis*-azido alcohol **rac-4** by treatment with sodium azide,

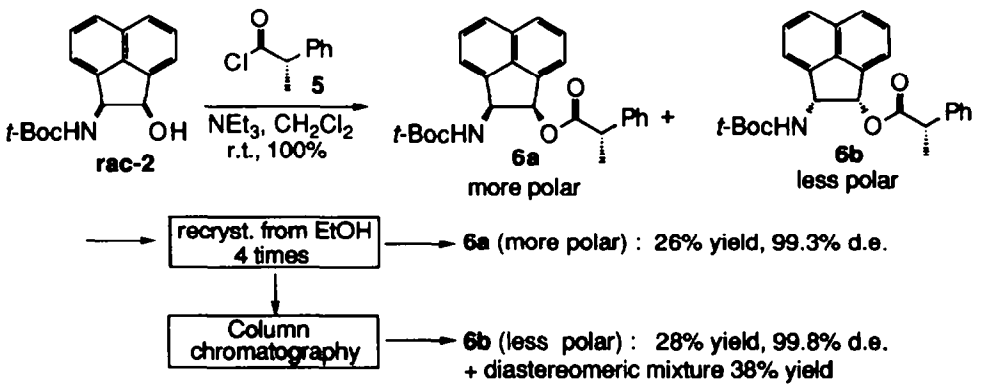
Scheme 2



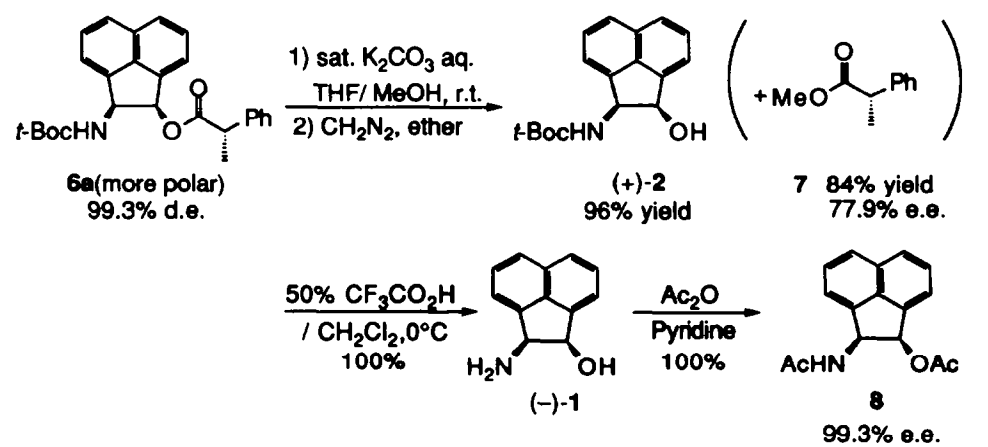
and hydrogenation (catalytic Pd/C, H_2, EtOH) of **rac-4** gave racemic *cis*-amino alcohol **rac-1** in 41% overall yield. This route provided a large amount of **rac-1** without the need for complete purification in each step.

Next, we investigated the resolution of amino alcohol **rac-1** in order to obtain enantiomerically pure **1**. *N*-Acylation with (*S*)-2-phenylpropionyl chloride gave an easily separable diastereomeric mixture of the corresponding amides. However, the hydrolysis of the amide bond under acidic conditions led to decomposition. Other deacylations, such as *O*-alkylation by the Meerwein reagent followed by hydrolysis and the half-reduction of the amide function, also resulted in failure. Therefore, we examined the resolution via esters prepared by the reaction of Boc-amino alcohol **rac-2** with homochiral acid chlorides. Among the homochiral acid chlorides examined, only (*S*)-2-phenylpropionyl chloride **5** was found to give a chromatographically separable diastereomeric mixture (Scheme 3). Acylation of **rac-2** with homochiral **5** under mild conditions gave a diastereomeric mixture of esters **6a** and **6b** in quantitative yield. Although this mixture was separable by chromatography, it was found that the combination of recrystallization and column

Scheme 3



Scheme 4



chromatography was most practical. Recrystallization of a diastereomeric mixture of **6a** and **6b** four times from ethanol gave the more polar (less soluble) diastereomer **6a** in 26% yield with 99.3% d.e. Separation of the concentrated filtrate by flash column chromatography gave the less polar diastereomer **6b** in 28% yield with 99.8 % d.e. and a mixture of both diastereomers (38%).

Each homochiral Boc-amino alcohol **2** was liberated by treatment with a saturated aqueous potassium carbonate solution (Scheme 4). The Boc group was removed with trifluoroacetic acid to afford optically active **1** in quantitative yield. The enantiomeric purity was confirmed on the basis of the chiral column HPLC analysis of *N,O*-diacetylated products **8** for both enantiomers. The analysis revealed that (–)-**1** obtained from **6a** (99.3% d.e.) was 99.3% e.e. without any racemization nor epimerization. However, recovered methyl 2-phenylpropionate **7** (84% yield), which was obtained by treatment of a crude reaction mixture with diazomethane, was racemized to some extent (77.9% e.e.).

The absolute configuration of amino alcohol (–)-**1** was determined by a single-crystal X-ray structural analysis of diastereomeric ester **6a** (Fig. 1). On the basis of the absolute configuration of (*S*)-2-phenylpropionic acid, the absolute configuration of (–)-**1** was determined to be 1*R*,2*S*.

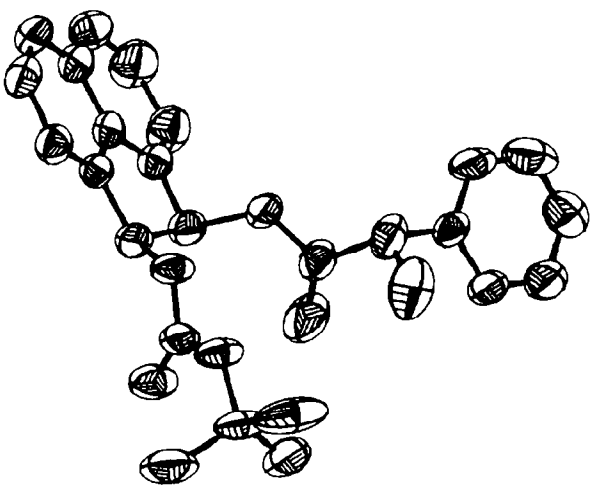


Figure 1. ORTEP Drawing of **6a**

With enantiomerically pure **1** in hand, we then applied this novel chiral auxiliary to the diastereoselective [2,3]-Wittig sigmatropic rearrangement,[10] since among several kinds of chiral auxiliaries reported thus far, a chiral oxazoline protocol is known to be very efficient.[11] 2-Chloromethyloxazoline **10**, synthesized from **rac-1** and imino ether hydrochloride **9**, was allowed to react with potassium salts of the required allylic alcohols to give the corresponding 2-(allyloxy)methyloxazolines **11a-d** (Scheme 5, Table 1.).

Scheme 5

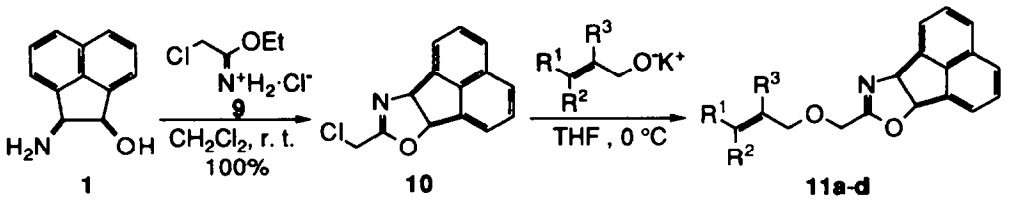


Table 1. Yields of Oxazolines **11**

	R^1	R^2	R^3	yield / %
11a	H	H	H	81
11b	Me	H	H	86
11c	Me	Me	H	65
11d	H	H	Me	84

In order to elucidate the effect of the counter cation of an azaenolate, **11a** was treated with butyllithium in tetrahydrofuran at -78 °C in the presence of various kinds of metal halides (KBr, $MgCl_2$, Cp_2TiCl_2, Cp_2ZrCl_2, $ZnBr_2$, $SnCl_4$, $CuCl_2$). However, the diastereoselectivity was not affected by the counter cation and therefore,

Scheme 6

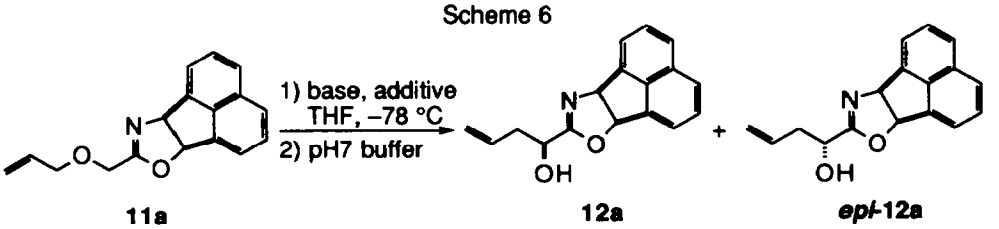


Table 2. Reactions of **11a** Under Various Conditions

Entry	Base	Additive	Yield / %	**12a**:*epi*-**12a** [a]
1	*n*-BuLi	–	58	73:27
2	*t*-BuLi	–	44	66:34
3	LDA	–	52	79:21
4		HMPA	35	77:23
5		TMEDA	64	76:24
6 [b]	LHMDS	–	10	80:20
7 [b]		TMEDA	55	79:21

a) Determined by 400 MHz ^{1}H-NMR.

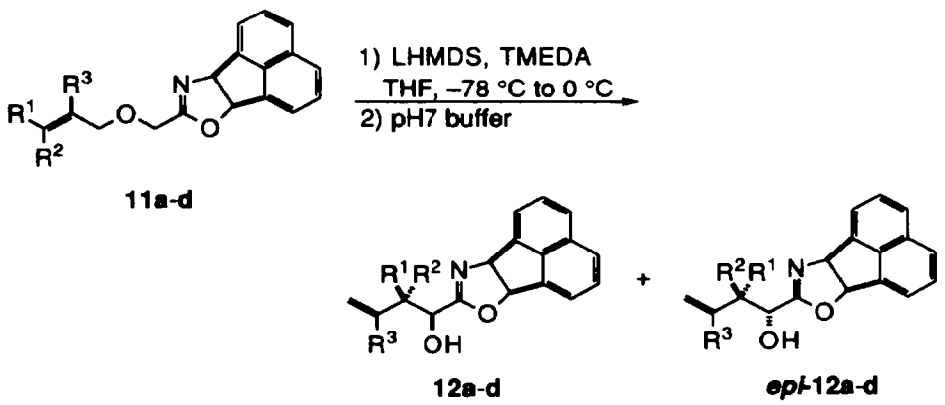
b) The reaction temperature was allowed to raise from –78 °C to 0 °C.

Li was used. Next, various kinds of lithium-bases and additives were examined. The results are summarized in Table 2.

Among the bases examined, the highest selectivity was achieved when lithium hexamethyldisilazide (LHMDS) was used (Table 2, entry 6). In the course of this study, other solvents, such as ether, hexane, and dimethoxyethane were also used, but only depression of the selectivity resulted. Because of the relatively low basicity of LHMDS, the reaction did not proceed at –78 °C and the reaction temperature was allowed to raise from –78 °C to 0 °C. Moreover, the addition of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) remarkably improved the chemical yield without serious depression of the diastereoselectivity (entries 5 vs 3 and entries 7 vs 6). To the contrary, the addition of hexamethylphosphoric triamide (HMPA) decreased the chemical yield (entries 4 vs 3).

Under the optimized reaction conditions, the reaction of **11** was carried out (Scheme 7), and the results are summarized in Table 3.

Scheme 7



11a-d **12a-d** ***epi*-12a-d**

Table 3. Reactions of Various Kinds of Allyl Ether Substrates **11**

Entry	**11**	R^1	R^2	R^3	Yield / %	**12**:***epi*-**12**
1	**11a**	H	H	H	55	79:21
2	**11b**	Me	H	H	73	75(98:2[a]):25(96:4[a])
3	**11c**	Me	Me	H	75	59[b]:41
4	**11d**	H	H	Me	62	82:18

a) *Erythro* :*threo* ratio. b) The relative configuration was determined by X-ray crystallography.

The relative stereochemistries of major product **12c** (entry 3) were determined by a X-ray crystallographic analysis (Fig. 2). The relative stereochemistries of the other major products were correlated with that of **12c** by the ^{1}H-NMR spectral data. In all cases, the chemical shift of the α-proton of the oxazoline in the major product

was higher than that of the minor product. This difference in chemical shift can be explained as follows: The hydrogen bonding between the hydroxyl group and the nitrogen atom in the oxazoline ring is assumed to fix the conformation. Therefore, Hα of the major product is more shielded by the naphthalene ring than that of the minor product (Fig. 3).

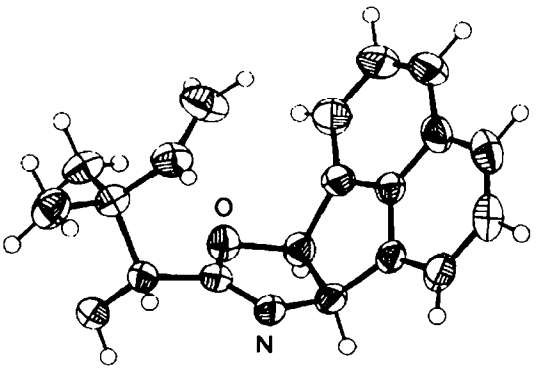


Figure 2. ORTEP Drawing of **12c**

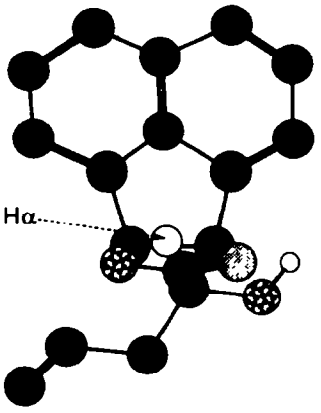


Figure 3. Most Stable Conformation of **12a**[12]

In the reaction of **11b** (entry 2), four diastereomers resulted, and the relative stereochemistry of major isomers of **12b** and ***epi*-12b** was determined to be *erythro* by the comparison of their ^{1}H-NMR data with that of the rearrangement products obtained from achiral 2-(2-propenyloxy)methyloxazoline.[13]

Several characteristics are evident from these data. 1) Unexpectedly, the introduction of R^1 and R^2 decreases the diastereoselectivity. 2) In entry 2, *erythro* selectivity is very high. 3) The introduction of R^3 increases the selectivity. These tendencies are explained by a transition state model, which is almost the same as Nakai's model,[11] with the oxazoline ring in the pseudo-axial position to prevent the gauche repulsive interaction between R^1 and the oxazoline ring (Fig. 4). The high *erythro* selectivity of the crotyloxy derivative is explained to be enhanced by the bulkiness of the chiral auxiliary. Kinetically, model **13** is preferred, in which Li chelates the ether oxygen of the Z-azaenolate, and the allyl group migrates from the bottom side of the enolate. When TMEDA was used as an additive, model **13** is considered to be more stabilized by a chelation between Li and two nitrogen atoms of TMEDA. The fact that the introduction of alkyl groups to the allyl terminus leads to a decrease in selectivity indicates the existence of *E*-*Z* isomerization of the azaenolate. When the allyl terminus is more substituted, the *E*-enolate is supposed to be formed before the reaction proceeds. As shown in model **15**, the bottom-side rearrangement of the *E*-enolate leads to the minor product. Another pathway to produce the minor product is shown in model **14**, although in this model R^3 is close to the naphthalene ring. When R^3 is Me, the repulsive interaction prevents the top-side rearrangement via **14** to increase the diastereofacial selectivity.

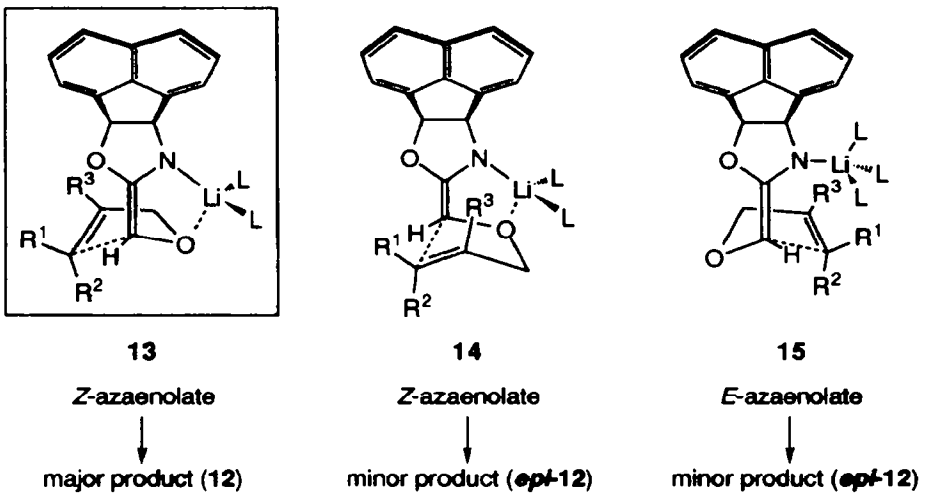


Figure 4. Transition State Models

Conclusion:

cis-2-Amino-1-acenaphthenol has been synthesized and resolved. This new homochiral amino alcohol was converted into an oxazoline ring, and the oxazoline was found to be useful chiral auxiliary in the [2,3]-Wittig rearrangement. This result would be valuable for designing a new chiral auxiliary.

EXPERIMENTAL SECTION

General Methods.

The melting points are not corrected. The ^{1}H-NMR spectra were measured on a FT spectrometer (JEOL JNM-GX400 or EX270) or on a continuous-wave instrument (JEOL JNM-PMX60si). The δ values are given in ppm with Me_4Si as an internal standard, and coupling constants (J) are given in hertz. The IR spectra were recorded on a JASCO IR-810 Infrared Spectrometer, and the unit for the values of IR spectra is cm^{-1}. The low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV on a Shimadzu QP-2000 and a JEOL JMS-AX505H, respectively. The X-ray crystal structure analysis was carried out by intensity measurement on a MAC Science MXC18 four-circle diffractometer, and structural solution and refinement by CRYSTAN.

All the moisture-sensitive reactions were carried out under Ar. THF, diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. All the other reagents and solvents were purified according to standard convention. The column chromatography was performed with E. Merck silica gel 60 (70-230 or 230-400 mesh). The preparative TLC (PTLC) was carried out with Wakogel B-5F.

Racemic *cis*-*N*-*tert*-Butoxycarbonyl-2-amino-1-acenaphthenol (rac-2). *tert*-Butyl *N*-chloro-*N*-sodiocarbamate[8] (4.09 g, 23.6 mmol) and silver nitrate (8.03 g, 43.2 mmol) in 200 ml of acetonitrile were stirred for 5 min at room temperature. To the resulting cream-yellow suspension was added acenaphthylene (2.34 g, 15.7 mmol). After 5 min, to this suspension was added an aqueous osmium tetroxide solution (2.7 wt%, 4.15 g, 0.66 mmol). After the reaction mixture (gray-brown colored) was stirred for 20 h at room temperature, 30 ml of saturated $NaHSO_3$ solution was added, and the reaction mixture was stirred for 12 h. After evaporation of acetonitrile, the product was extracted with AcOEt (100 ml × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction product was purified by short column chromatography (silica gel 60, 70-230 mesh, CH_2Cl_2) and recrystallization (hexane:benzene 1:1, 200 ml) to give **rac-2** (1.96 g, 6.78 mmol, 44%) as a white solid: Mp 156.7-157.5 °C; IR (KBr) 3430, 2990, 2880, 1695, 1520, 1180, 1170, 785; ^{1}H-NMR (270 MHz; $CDCl_3$) 1.51 (9H, s), 2.56 (1H, br d), 5.24 (1H, br d), 5.50 (1H, dd, *J*=5.9, 7.9), 5.60 (1H, dd, *J*=5.9, 6.1), 7.47-79 (6H, m). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.52; H, 6.74; N, 5.00.

Racemic *cis*-2-Amino-1-acenaphthenol (rac-1).

Method A: To a solution of **rac-2** (1.95 g, 6.83 mmol) in dichloromethane (50 ml) was added 50 ml of trifluoroacetic acid at 0 °C. After being stirred for 2 h, the reaction mixture was poured into 300 ml of 3 N KOH solution. The layers were separated, and aqueous layer was extracted with dichloromethane (50 ml × 3). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to give **rac-1** (1.01 g, 5.45 mmol, 85%) as a white solid, which immediately turns to a greenish amorphous mass under air: ^{1}H-NMR (60 MHz; DMSO-d6) 3.3 (3H, br s), 4.6 (1H, d, *J*=6.0), 5.2 (1H, d, *J*=6.0). Further purification and spectral data acquisition were carried out after derivation into its cinnamic acid salt (a white solid): Mp 158.7-159.2 °C; IR (KBr) 3450, 1640, 1562, 1550, 1390, 780, 720, 690; ^{1}H-NMR (270 MHz; $CDCl_3$+DMSO-d6) 4.50 (4H, br s), 4.87 (1H, br d, *J*=6.0), 5.63 (1H, d, *J*=6.3), 6.45 (1H, d, *J*=15.8), 7.47-79 (12H, m). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.57; H, 5.76; N, 4.18.

Method B: To a solution of acenaphthylene (1.00 g, 6.57 mmol) in 20 ml of dimethylsulfoxide was added *N*-bromosuccinimide (2.34 g, 13.4 mmol) in one portion under Ar at 0 °C. Upon removal of the ice-bath, the reaction temperature rose to ca. 60 °C. After stirring for 20 min at room temperature, the orange-colored reaction mixture was poured into 200 ml of cold water and extracted with ether (100 ml × 3). Evaporation of the solvent and short column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 95:5) gave 1.00 g of crude racemic *trans*-bromohydrin **rac-3** as a viscous brown oil: ^{1}H-NMR (60 MHz; $CDCl_3$) 2.6 (1H, br s), 5.5 (1H, d, *J*=2.0), 5.9 (1H, d, *J*=2.0), 7.5-7.9 (6H, m). To a solution of this crude **rac-3** in 50 ml of dimethylsulfoxide was added sodium azide (1.3 g, 20 mmol). The reaction mixture was stirred at 70 °C for 30 min, poured into 300 ml of cold water, and extracted with ether (100 ml × 3). The combined extracts were dried over Na_2SO_4 and filtered. Evaporation of the solvent gave 670 mg of crude racemic *cis*-azido alcohol **rac-4** as a pale yellow crystal: ^{1}H-NMR (60 MHz; $CDCl_3$) 2.9 (1H, d, *J*=8.0), 5.1 (1H, d, *J*=8.0), 5.6 (1H, dd, *J*=7.0, 8.0), 7.5-8.0 (6H, m). This crude **rac-4** was dissolved in 50 ml of ethanol, and palladium-charcoal (5%, 0.15g) was added to the solution. The reaction mixture was stirred under a hydrogen atmosphere for 12 h, and the catalyst was filtered off. Evaporation of ethanol gave 500 mg of **rac-1** (2.70 mmol, 41% from acenaphthylene).

Optical Resolution of rac-2. To a solution of **rac-2** (1.72 g, 6.03 mmol) and 1 ml of pyridine in dichloromethane (80 ml), was added a solution of (*S*)-2-phenylpropionyl chloride **5** in dichloromethane (20 ml) drop by drop over a period of 5 min under Ar at 0 °C. After being stirred for 1 h at 0 °C, saturated $NaHCO_3$ solution (20 ml) was added, and the reaction mixture was extracted with dichloromethane (20 ml × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction product was purified by column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 10:1) to give 2.41 g (6.03 mmol, 100%) of a diastereomeric mixture of esters **6a** and **6b** as a white solid. Recrystallization of this diastereomeric mixture (764 mg, 2.68 mmol) from 7.5 ml of ethanol 4 times gave 198 mg (0.694 mmol, 26%) of more polar (less soluble) ester **6a** (99.3% d.e.) as colorless needles. Separation of the concentrated filtrate by flash column chromatography (silica gel 60, 230-400 mesh, hexane:AcOEt 30:1) gave 215 mg (0.754 mmol, 28%) of less polar diastereomer **6b** (99.8% d.e.) and a mixture of both diastereomers (38%). The diastereomeric excesses of both **6a** and **6b** were determined by HPLC analysis (Merck LiChrosphere, hexane:AcOEt 10:1, α 1.17).

(1*R*,2*S*)-*N*-*tert*-Butoxycarbonyl-2-amino-1-acenaphthenyl (*S*)-2-phenylpropionate (6a). Mp 163.5-163.8 °C; $[\alpha]_D^{21.6}$–107.7 ($CHCl_3$, c 1.50); ^{1}H-NMR (270 MHz; $CDCl_3$) 1.50 (9H, s), 1.53 (3H, d, *J*=5.5), 3.77(3H, d, *J*=5.5), 4.97 (1H, d, *J*=9.5), 5.82 (1H, dd, *J*=7.6, 9.5), 6.61 (1H, d, *J*=7.6), 7.20-80 (11H, m); IR (KBr) 3450, 2980, 1730, 1695, 1510, 1245, 1150, 770, 695. Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.91; H, 6.60; N, 3.45. X-ray crystallographic details: $C_{26}H_{27}NO_4$, FW=417.0, monoclinic, space group $P2_1$, a=16.337(8)Å, b=5.282(3)Å, c=13.008(7)Å, V=1103(1)Å^3, β=100.82(4)°, R=0.051, Rw=0.064.

(1*S*,2*R*)-*N*-*tert*-Butoxycarbonyl-2-amino-1-acenaphthenyl (*S*)-2-phenylpropionate (6b). Mp 122.7-123.3 °C; $[\alpha]_D^{21.2}$+89.9 ($CHCl_3$, c 1.50); ^{1}H-NMR (270 MHz; $CDCl_3$) 1.48 (9H, s), 1.51 (3H, d, *J*=5.9), 3.68 (3H, d, *J*=5.9), 4.81 (1H, d, *J*=8.4), 5.81 (1H, dd, *J*=7.6, 8.4), 6.59 (1H, d, *J*=7.6), 7.22-82 (11H, m); IR (KBr) 3450, 2980, 1732, 1695, 1520, 1250, 1180, 780, 700. Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.84; H, 6.53; N, 3.60.

(1*R*,2*S*)-(+)-2. To a solution of **6a** (375.5 mg, 0.899 mmol) in THF (4 ml) and methanol (4 ml) was added 4 ml of saturated K_2CO_3 solution at room temperature, and the suspension was vigorously stirred at room temperature for 2 h. The reaction mixture was acidified with 100 ml of 3 N HCl and extracted with dichloromethane (30 ml × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining residue was dissolved in ether (20 ml) and treated with excess amount of diazomethane (ether solution). Evaporation of ether, followed by column chromatography (silica gel 60, 70-230 mesh, hexane:dichloromethane 1:2), gave methyl 2-phenylpropionate (*S*)-**7** (123.6 mg, 0.753 mmol, 84%), of which the optical purity was determined to be 77.9% e.e. by chiral HPLC (Dicel Chiralcel OJ, hexane:2-propanol 9:1, α 1.20) and (+)-**2** (251.8 mg, 0.882 mmol, 99%): Mp 167.0-167.5 °C; $[\alpha]_D^{22.8}$+12.3 ($CHCl_3$, c 1.55). The other spectral data were identical with those of **rac-2**.

(1*S*,2*R*)-(−)-2. Treatment of **6b** (100.2 mg, 0.240 mmol) by a similar procedure described for **(1*R*,2*S*)-(+)-2** yielded 64.3 mg (0.225 mmol, 94%) of **(1*S*,2*R*)-(−)-2**: Mp 167.0-167.5 °C; $[\alpha]_D^{22.8}$–12.3 ($CHCl_3$, c 1.50). The other spectral data were identical with those of **rac-2**.

(1*R*,2*S*)-(−)-1. To a solution of (+)-**2** (116.3 mg, 0.408 mmol) in dichloromethane (5 ml) was added 5 ml of trifluoroacetic acid at 0 °C. After being stirred for 2 h, the reaction mixture was poured into 30 ml of 3 N KOH, and the solution was extracted with dichloromethane (10 ml × 3). The combined extracts were dried

over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to give **(1*R*,2*S*)-(−)-1** (75.5 g, 0.408 mmol, 100%); $[\alpha]_D^{17.6}$–26.8 (MeOH, c 2.10). Further purification and spectral data acquisition were carried out after derivation into its cinnamic acid salt: Mp 165.8-166.3 °C; $[\alpha]_D^{22.0}$+7.4 (MeOH, c 1.00). The other spectral data were identical with those of the cinnamic acid salt of **rac-1**. Obtained **(1*R*,2*S*)-(−)-1** was converted into its *N*,*O*-diacetylated derivative by treatment with pyridine and acetic anhydride at room temperature, whose enantiomeric purity was determined to be 99.3% e.e. by chiral HPLC (Dicel Chiralcel OD, hexane:2-propanol 9:1, α 1.69, lower *Rf*).

(1*S*,2*R*)-(+)-1. Treatment of **(−)-2** (73.1 mg, 0.256 mmol) by a similar procedure described for the preparation of **(1*R*,2*S*)-(−)-1** yielded 44.0 mg (0.238 mmol, 93%) of **(1*S*,2*R*)-(+)-1**: $[\alpha]_D^{18.0}$+24.3 (MeOH, c 1.00). Further purification and spectral data acquisition were carried out after derivation into its cinnamic acid salt: Mp 165.8-166.4 °C; $[\alpha]_D^{22.0}$–7.4 (MeOH, c 1.00). The other spectral data were identical with those of the cinnamic acid salt of **rac-1**. Obtained **(1*S*,2*R*)-(+)-1** was converted into its *N*,*O*-diacetylated derivative by treatment with pyridine and acetic anhydride at room temperature, whose enantiomeric purity was determined to be 99.8% e.e. by chiral HPLC (Dicel Chiralcel OD, hexane:2-propanol 9:1, α 1.69, higher *Rf*).

(6b*R,9a*S**)-8-Chloromethyl-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole 10**. To a solution of **rac-1** (425 mg, 2.29 mmol) and ethyl 2-chloroacetimidate hydrochloride **9** (362 mg, 2.29 mmol) in 30 ml of CH_2Cl_2 was added 0.5 ml of triethylamine at room temperature under Ar, and the reaction mixture was stirred at that temperature for 17 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 4:1) to give 561 mg (2.29 mmol, 100%) of **10** as a cream-white solid: Mp 132.0-133.0 °C; *Rf* 0.6 (hexane:AcOEt 1:1); IR (KBr) 1660, 1340, 1268, 1162, 1033, 963, 940; ^{1}H-NMR (270 MHz; $CDCl_3$) 4.06 (2H, dd, *J*=13.2, 22.4), 6.04 (1H, d, *J*=7.6), 6.36 (1H, d, *J*=7.3), 7.54-7.84 (6H, m); EI-MS 84 (44.2), 140 (39.0), 166 (100.0), 243 (M^+, 41.8); HR-MS calcd for $C_{14}H_{10}ClNO$ 243.0451, found 243.0434.

(6b*R,9a*S**)-8-(2-Propenyloxy)-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (11a)**. Under Ar, KH (53.1 mg, 1.32 mmol, mineral oil dispersion) was washed with hexane (2 ml × 3), and 1 ml of THF was added. To this suspension was added allyl alcohol (93.2 mg, 1.60 mmol) drop by drop over a period of 5 min at 0 °C. After the solution was stirred for 30 min at room temperature, **10** (269 mg, 1.10 mmol) in 2 ml of THF was added drop by drop over a period of 10 min at 0 °C, and the mixture was allowed to warm to room temperature and stirred for additional 30 min. The reaction was quenched by adding 10 ml of water. The solution was extracted with CH_2Cl_2 (10 ml × 3) and purified by column chromatography (silica gel 60, 70-230 mesh, hexane:AcOEt 4:1) to give 235 mg (0.887 mmol, 81%) of **11a** as a pale yellow syrup: *Rf* 0.38 (hexane:AcOEt 1:1); IR (neat) 1670, 1105, 972, 937, 835, 786; ^{1}H-NMR (400 MHz; $CDCl_3$) 4.01 (2H, m), 4.10 (2H, s), 5.14 (1H, dd, *J*=3.1, 10.4), 5.21 (1H, dd, *J*=3.1, 17.4), 5.85 (1H, m), 6.00 (1H, d, *J*=7.6), 6.28 (1H, d, *J*=7.3), 7.54-7.82 (6H, m); EI-MS 140 (30.7), 152 (100.0), 167 (71.0), 265 (M^+, 25.0); HR-MS calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1095.

(6b*R,9a*S**)-8-[(*E*)-2-Butenyloxy]-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (11b)**. A similar procedure described for the preparation of **11a** was applied and yielded **11b** (86%) as a pale yellow syrup by using 2-buten-1-ol (*E*:*Z*>99:1) as an alcohol. The *E*:*Z* ratio of **11b** was determined to be 98:2 by ^{1}H-NMR (400 MHz): *Rf* 0.40 (hexane:AcOEt 1:1); IR (neat) 1665, 1110, 970, 932, 835, 785; ^{1}H-NMR (400 MHz; $CDCl_3$) 1.51 (3H×0.98, d, *J*=7.0), 1.63 (3H, dd, *J*=1.5, 6.2), 3.93 (2H, m), 4.08 (2H, s), 5.51 (1H,

dt, *J*=7.0, 15.4), 5.65 (1H, dd, *J*=6.2, 15.4), 6.00 (1H, d, *J*=7.7), 6.29 (1H, d, *J*=7.7), 7.52-7.82 (6H, m); EI-MS 55 (40.5), 140 (21.7), 152 (100.0), 167 (78.6), 194 (16.9), 209 (16.9), 279 (M^+, 17.7); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1261.

(6b*R,9a*S**)-8-(3-Methyl-2-butenyloxy)-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (11c).** A similar procedure described for the preparation of **11a** was applied and yielded **11c** (65%) as a pale yellow syrup by using 3-methyl-2-buten-1-ol as an alcohol: *Rf* 0.60 (hexane:AcOEt 1:1); IR (neat) 1660, 1100, 965, 925, 832, 793; ^{1}H-NMR (270 MHz; $CDCl_3$) 1.53 (3H, s), 1.66 (3H, s), 3.98 (2H, d, *J*=7.3), 4.08 (2H, s), 5.28 (1H, t, *J*=7.3), 6.00 (1H, d, *J*=7.6), 6.28 (1H, d, *J*=7.6), 7.56-7.82 (6H, m); EI-MS 69 (25.5), 139 (18.5), 152 (92.2), 167 (100.0), 194 (16.2), 209 (32.7), 293 (M^+, 12.5); HR-MS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1428.

(6b*R,9a*S**)-8-(2-Methyl-2-propenyloxy)-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (11d).** A similar procedure described for the preparation of **11a** was applied and yielded **11d** (84%) as a pale yellow syrup by using 2-methyl-2-propen-1-ol as an alcohol: *Rf* 0.50 (hexane:AcOEt 1:1); IR (neat) 1660, 1100, 1018, 970, 905, 830, 792; ^{1}H-NMR (270 MHz; $CDCl_3$) 1.67 (3H, s), 3.92 (2H, dd, *J*=12.4, 16.8), 4.07 (2H, s), 4.84 (1H, d, *J*=2.0), 4.89 (1H, d, *J*=2.0), 6.01 (1H, d, *J*=7.3), 6.29 (1H, d, *J*=7.6), 7.50-7.83 (6H, m); EI-MS 55 (27.9), 139 (21.2), 152 (100.0), 194 (20.0), 194 (18.3), 279 (M^+, 15.6); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1239.

The General Procedure for the [2,3]-Wittig Rearrangement of 11. The general procedure is exemplified for the reaction of **11c**. To a stirred solution of 118 mg (0.734 mmol) of TMS_2NH in THF (2 ml) at –78 °C was added *n*-BuLi (0.34 ml, 1.61 M, 0.54 mmol) drop by drop over a period of 1 min. After 30 min, a solution of TMEDA (94.4 mg, 0.812 mmol) in THF (1 ml) was added drop by drop over a period of 3 min at -78 °C, and the solution was stirred for 25 min. At –78 °C, a solution of **11c** (103 mg, 0.351 mmol) in THF (2 ml) was added to the reaction mixture drop by drop over a period of 10 min. Then, the reaction mixture was allowed to warm to 0 °C and stirred for 1.5 h. The reaction was quenched by adding 10 ml of pH 7 buffer. The solution was extracted with CH_2Cl_2 (10 ml × 3). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by PTLC (hexane:AcOEt 2:1) to give 45.9 mg (45%) of **12c** (lower *Rf*) and 31.6 mg (31%) of ***epi*-12c**.

(6b*R,9a*S**)-8-[(*R**)-1-Hydroxy-3-butenyl]-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (12a).** Obtained as a mixture with ***epi*-12a** (**12a**:***epi*-12a** 79:21, determined by ^{1}H-NMR): Mp 179.7-182.5 °C; *Rf* 0.40 (hexane:AcOEt 1:2); IR (KBr) 3400, 1660, 1180, 1100, 978, 922, 833, 782; ^{1}H-NMR (400 MHz; $CDCl_3$) 2.35 (2H × 0.21, m), 2.50 (2H × 0.79, m), 2.95 (1H × 0.21, br s), 3.00 (1H × 0.79, br s), 4.27 (1H × 0.79, pseudo q, *J*=7.1), 4.36 (1H × 0.21, pseudo q, *J*=7.1), 4.80 (2H × 0.21, m), 5.10 (2H × 0.79, m), 5.51 (1H × 0.21, m), 5.56 (1H × 0.79, m), 5.94 (1H × 0.21, d, *J*=7.2), 5.96 (1H × 0.79, d, *J*=7.2), 6.31 (1H × 0.21, d, *J*=7.2), 6.32 (1H × 0.79, d, *J*=7.2), 7.58-7.82 (6H, m); EI-MS 69 (11.7), 139 (20.7), 152 (100.0), 168 (40.0), 194 (17.8), 265 (M^+, 24.7); HR-MS calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1115.

(6b*R,9a*S**)-8-[(1*R**,2*S**)-1-Hydroxy-2-methyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (12b).** Obtained as a mixture of *erythro*- and *threo*-isomers (*erythro*:*threo* 98:2, determined by ^{1}H-NMR): White solid; mp 131.5-133.0 °C; *Rf* 0.44 (hexane:AcOEt 1:2); IR (KBr) 3200, 1680, 1228, 1062, 977, 920, 832, 788; ^{1}H-NMR (400 MHz; $CDCl_3$) 1.03 (3H × 0.98, d, *J*=7.0), 1.10 (3H × 0.02, d, *J*=7.0), 2.60 (1H, m), 2.76 (1H, br s), 4.08 (1H × 0.02, t, *J*=4.8), 4.17 (1H × 0.98, t, *J*=5.0), 4.94 (1H, d, *J*=12.3), 5.01 (1H, d, *J*=19.7), 5.77 (1H, m), 5.98 (1H, d, *J*=7.3), 6.34 (1H, d, *J*=7.3), 7.52-7.83 (6H, m);

EI-MS 139 (15.3), 152 (100.0), 168 (36.6), 194 (14.0), 279 (M^+, 18.4); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1269.

(6b*R,9a*S**)-8-[(1*S**,2*R**)-1-Hydroxy-2-methyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (*epi*-12b).** Obtained as a mixture of *erythro*- and *threo*-isomers (*erythro*:*threo* 96:4, determined by ^{1}H-NMR). White solid; mp 157.8-159.2 °C; *Rf* 0.53 (hexane:AcOEt 1:2); IR (KBr) 3175, 1677, 1040, 957, 8323, 780; ^{1}H-NMR (400 MHz; $CDCl_3$) 0.70 (3H × 0.96, d, *J*=6.7), 0.94 (3H × 0.04, d, *J*=7.0), 2.47 (1H, m), 2.72 (1H, d, *J*=5.2), 4.18 (1H × 0.04, t, *J*=5.1), 4.25 (1H × 0.96, t, *J*=5.3), 4.82 (1H, d, *J*=10.5), 4.88 (1H, d, *J*=19.3), 5.63 (1H, m), 5.95 (1H, d, *J*=7.3), 6.32 (1H, d, *J*=7.3), 7.52-7.83 (6H, m); EI-MS 139 (15.1), 152 (100.0), 168 (39.5), 194 (12.4), 279 (M^+, 14.8); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1250.

(6b*R,9a*S**)-8-[(*R**)-1-Hydroxy-2,2-dimethyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (12c).** White solid; mp 131.8-132.0 °C; *Rf* 0.45 (hexane:AcOEt 1:2); IR (KBr) 3200, 1643, 1078, 980, 838, 782; ^{1}H-NMR (400 MHz; $CDCl_3$) 0.99 (3H, s), 1.04 (3H, s), 2.82 (1H, d, *J*=6.3), 3.93 (1H, d, *J*=6.1), 4.97 (1H, d, *J*=14.3), 5.00 (1H, d, *J*=10.7), 5.83 (1H, dd, *J*=10.0, 14.4), 5.94 (1H, d, *J*=7.3), 6.28 (1H, d, *J*=7.3), 7.52-7.81 (6H, m); EI-MS 139 (10.5), 152 (100.0), 168 (34.2), 194 (12.7), 293 (M^+, 11.9); HR-MS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1428. X-ray crystallographic details: $C_{19}H_{19}NO_2$, FW=293.0, orthorhombic, space group $P2_12_12_1$, *a*=10.136(1)Å, *b*=26.755(3)Å, *c*=5.6996(8)Å, *V*=1545.6(4)Å^3, β=100.82(4)°, *R*=0.045, *Rw*=0.050.

(6b*R,9a*S**)-8-[(*S**)-1-Hydroxy-2,2-dimethyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno-[1,2-*d*]oxazole (*epi*-12c).** White solid; mp 132.0-132.3 °C; *Rf* 0.60 (hexane:AcOEt 1:2); IR (KBr) 3150, 1643, 1068, 975, 830, 781; ^{1}H-NMR (400 MHz; $CDCl_3$) 0.85 (3H, s), 0.87 (3H, s), 2.80 (1H, br s), 3.98 (1H, s), 4.66 (1H, d, *J*=14.4), 4.75 (1H, d, *J*=9.8), 5.63 (1H, dd, *J*=9.8, 14.6), 5.94 (1H, d, *J*=7.3), 6.29 (1H, d, *J*=7.3), 7.50-7.81 (6H, m); EI-MS 139 (9.9), 152 (100.0), 168 (37.7), 194 (10.4), 293 (M^+, 11.7); HR-MS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1430.

(6b*R,9a*S**)-8-[(*R**)-1-Hydroxy-3-methyl-3-butenyl]-2*H*[6b,9a]-acenaphthyleno[1,2-*d*]oxazole (12d).** Obtained as a mixture with ***epi*-12d** (**12d**:***epi*-12d** 82:18, determined by ^{1}H-NMR): Mp 115.0-119.0 °C; *Rf* 0.50 (hexane:AcOEt 1:2); IR (KBr) 3280, 1660, 1105, 1065, 904, 814, 783; ^{1}H-NMR (400 MHz; $CDCl_3$) 1.58 (3H × 0.82, s), 1.72 (3H × 0.18, s), 2.31 (2H × 0.82, m), 2.40 (2H × 0.18, m), 2.62 (1H × 0.82, br s), 3.01 (1H × 0.18, br s), 4.35 (1H × 0.18, m), 4.43 (1H × 0.82, m), 4.64 (2H × 0.82, d, *J*=19.0), 4.80 (2H × 0.18, d, *J*=30.0), 5.93 (1H × 0.18, d, *J*=7.3), 5.98 (1H × 0.82, d, *J*=7.3), 6.32 (1H, d, *J*=7.3), 7.60-7.82 (6H, m); EI-MS 55 (13.8), 139 (17.9), 152 (100.0), 167 (67.5), 194 (15.5), 278 (33.9), 279 (M^+, 29.4); HR-MS calcd for $C_{18}H_{17}NO_2$ 279.1259, found 279.1283.

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