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Synthesis and Biological Evaluation of Both Enantiomers of Dynemicin A Model Compound

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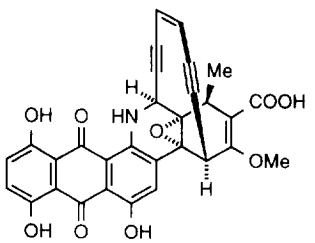
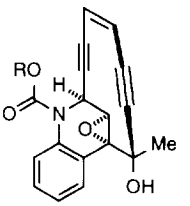
Abstract: A novel 1,4-asymmetric induction was developed for the synthesis of chiral dynemicin A model compound. By using this reaction, both enantiomers were synthesized from chiral alcohol prepared by lipase catalyzed resolution. The biological activities of these compounds were examined.

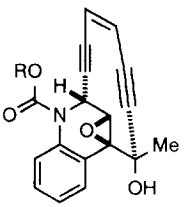
In recent years, a new class of potent antitumor antibiotics, called cyclic enediyne, has been reported.[1] Dynemicin A (**1**), one of the growing families in these antibiotics, has exhibited powerful antitumor activities.[2] The biological activities are believed to be responsible for radical DNA cleavage via Bergman cycloaromatization of enediyne moiety.[3,4] The structure of **1** was determined by a X-ray crystallographic analysis, while the absolute stereochemistry remained uncovered.[5] Molecular dynamics simulations between double strand DNA and dynemicin were reported to propose plausible absolute configuration as shown in **Figure 1**.[6] Nicolaou *et al.* reported that different cytotoxicities of their dynemicin A analogs against certain cell lines were due to these absolute stereochemistries.[7] Danishefsky *et al.* reported the significant difference between enantiomers of calicheamicinone (calicheamicin aglycon) in DNA cleaving abilities.[8] These results indicated that chirality of enediyne core moiety was important for interaction with DNA even though in the absence of specific DNA recognition sites such as intercalator, minor gloove binder. In connection with our studies on dynemicin A,[9, 10] we were interested in the difference of biological activities between both enantiomers of our model **2**, which was previously synthesized as a racemate.[11] We describe here the details of development of new asymmetric reaction for this purpose, synthesis of the both enantiomers of **2**,[12] and these biological activities.



Dynemicin A (1)



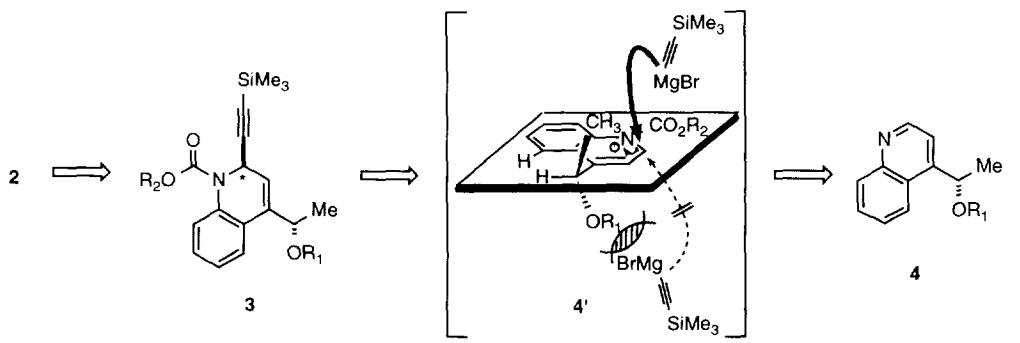
(+)-2



(-)-2

Figure 1

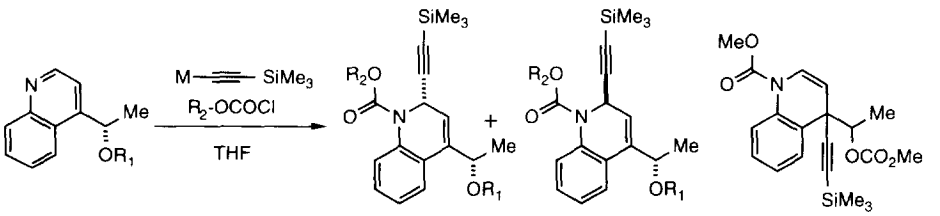
Our racemic compound (±)-**2** (R = Et) was synthesized from (±)-**4** via intermediate **3** (**Scheme 1**). All asymmetric centers in **2** were induced from the stereogenic center at propargylic position (*) in **3**. Employment of this route for chiral synthesis did request a new diastereoinductive addition of an acetylide induced by asymmetric center on quinoline side chain. We have found out a symptom of such selectivity in our racemic synthesis (R_1 = TBDMS, R_2 = Et), which was about 1 : 2. This selectivity was explained by followings: the most stable conformer was assumed to that shown in **4'** due to severe interaction between the C-4 side chain and the proton at *peri* position.[13] Thus, magnesium acetylide was predominantly introduced from less hindered side (the opposite side to bulky silylether). Consequently, larger protective group was expected to give better selectivity.



Scheme 1

Based on the above considerations, systematic search for the best reaction conditions [including protective groups (R_1) of hydroxy group, type (R_2) of carbamate, reaction temperatures] were performed using the racemic substrates.[14] The representative results are shown in **Table 1**. The substrate **5** bearing free hydroxy group gave a mixture of regioisomers [1,2-adduct **12** (37 %) and 1,4-adduct **13** (28 %)] (entry 1). Stereoselectivity of 1,2-adduct **12** was similar to that of the benzoate (entry 5), while 1,4-adduct **13** was a single stereoisomer although the configuration was not clear. MOM and MEM groups gave no selectivity (entry 2, 3), which excluded a chelation with magnesium ion. As expected, larger protective group showed better selectivity (entry 7). Examination on the type of carbamate revealed that phenyl chloroformate formed more reactive intermediate **4'** (acyl quinolinium ion) which resulted in fast completion of the addition reaction. This observation led us to examine the effect of reaction temperature. Finally the reaction at -78 °C was found to afford the best selectivity (entry 11). These results supported the above discussion on the conformation in proposed mechanism.[15]

The stirring time (at -78 °C) before the addition of phenyl chloroformate to the solution of **11** and magnesium acetylide was important in order to keep the best result as in entry 11. If the preliminary stirring time was shorter than 30 min, the selectivity decreased to about 1:8. Stirring over 2 h at -78 °C was required for keeping the highest selectivity (1:13). The stereochemistry of the major product was determined as *anti* by X-ray crystallographic analysis of **22** which was derived from **21** (**Scheme 3**). A Chem 3D drawing of the X-ray data of **22** is shown in **Figure 2**. This result supported the proposed transition state model as depicted in **Scheme 1**.[16]



Scheme 2

syn ***anti***

1,2-adduct

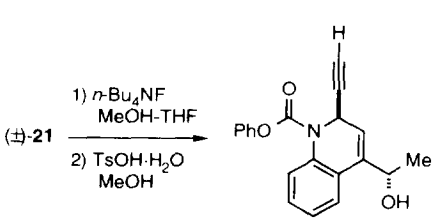
13 (28%)

1,4-adduct

Table 1

entry	substrate	R_1	M	R_2	temp	products (1,2-adduct)	yield (%)	***syn*** : ***anti*** [a]
1	**5**	H	MgBr	Me	0 °C	**12**	37 [b]	1 : 1.7
2	**6**	MOM	MgBr	Me	0	**14**	65	1 : 1.1
3	**7**	MEM	MgBr	Me	0	**15**	83	1 : 1.1
4	**8**	PMB	MgBr	Me	0	**16**	85	1 : 1.3
5	**9**	Bz	MgBr	Me	0	**17**	70	1 : 1.7
6	**10**	TES	MgBr	Me	0	**18**	63	1 : 1.5
7	**11**	TBDPS	MgBr	Me	0	**19**	85	1 : 2.3
8	**11**	TBDPS	MgBr	Bn	0	**20**	79	1 : 2.1
9	**11**	TBDPS	MgBr	Ph	0	**21**	100	1 : 4.9
10	**11**	TBDPS	MgBr	Ph	-20	**21**	100	1 : 5.6
11	**11**	TBDPS	MgBr	Ph	-78	**21**	87	1 : 13
12	**8**	PMB	$SnBu_3$	Ph	0 [c]	**23**	46	1.6 : 1
13	**10**	TBDPS	$SnBu_3$	Ph	0 [c]	**21**	20	2.4 : 1

[a] The ratio was determined by integration value of ^{1}H NMR. [b] The 1,4-adduct **13** (28%) was also obtained, see text. [c] CH_2Cl_2 was used instead of THF as solvent.



Scheme 3

22

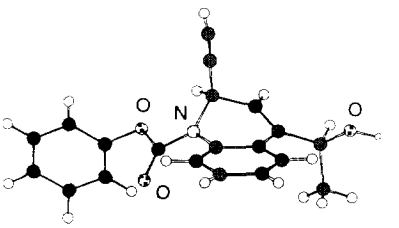
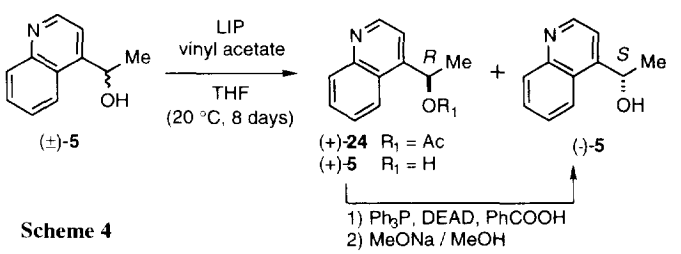


Figure 2

On the other hand, tin acetylide (ethynyltributyltin) instead of magnesium acetylide was found to give the opposite selectivity in the presence of phenyl chloroformate even though the yields were not so

high[17] (entry 12, 13 in **Table 1**). The difference of mechanisms between magnesium acetylide and the tin acetylide has not been clear.

Next problem was to prepare the starting alcohol in an optically active form. For the synthesis of both enantiomers, we decided to resolve the racemic alcohol **5**. Reports on preparative scale resolution of 1-(1'-naphthyl)ethanol by a lipase (PPL, Porcine Pancreatic Lipase)[18] promoted us to use the enzyme. The acylation of **5** under the same reaction conditions, however, gave the butyrate in a very low chemical yield (8 %) with high optical purity (94 % ee)[19] because of its extremely low solubility toward heptane used as a solvent. All attempts (reaction temperatures, solvents, acylation agents, etc.) to improve the yield with retaining the optical purity were unsuccessful. After screening some commercial available lipases,[20] we found that LIP (immobilized lipase from TOYOBO) gave the best result to obtain both enantiomers with high optical purities (**Scheme 4**). The yields of acetate (+)-**24** and alcohol (−)-**5** were 51 % (96 % ee) and 48 % (95 % ee), respectively. Although THF showed enough solubility to **5**, the catalytic activity of LIP was gradually lost during the reaction. So that portionwise addition of the enzyme was required to complete the resolution. Absolute configuration of the acetate (+)-**24** was determined as *R* by a modified Mosher's method[21] (**Figure 3**). The chiral alcohol **5** could be inverted with retaining the high optical purity (96 % ee → 96 % ee) by Mitsunobu reaction[22] and subsequent hydrolysis of the benzoate. This experiment showed that either of the chiral compounds was obtainable from each other.



Scheme 4

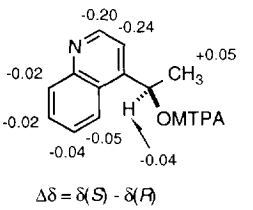
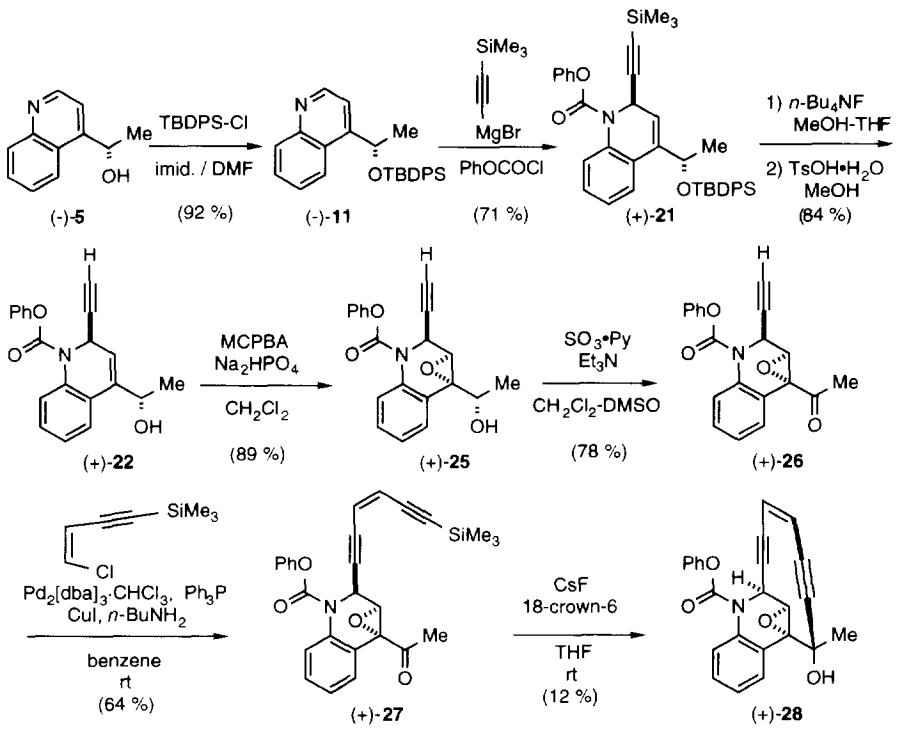


Figure 3

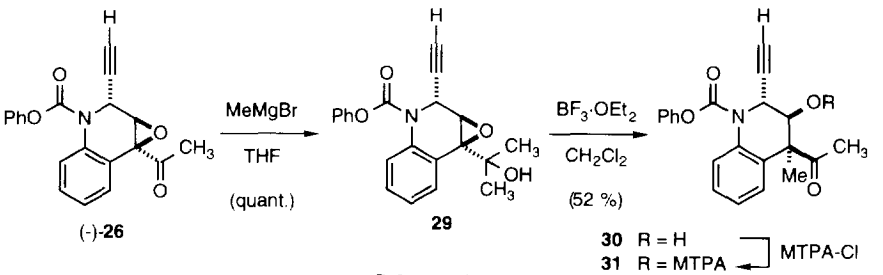
Having established the highly stereoselective reaction and preparation of chiral starting material, the model compound (+)-**28** was synthesized from (−)-**5** as shown in **Scheme 5** according to the racemic synthesis.[11] Opposite enantiomer (−)-**28** was also synthesized from (+)-**5** in the same manner. The stereochemistry of newly formed asymmetric center was determined by NOE observation between methyl and epoxy protons. In this sequence, it was worthwhile to note that epoxidation of **22** with MCPBA gave **25** as a single stereoisomer. This high stereoselectivity was contrast to that in our previous report.[10] Direct cyclization of silylacetylene **27** using fluoride anion[10c, 11] was still a poor process (12 %). This type of cyclization using attack of acetylide anion to carbonyl group was originally developed for the strained enediyne compounds by Danishefsky[23] and Kende,[24] and have been widely used for construction of enediyne compound as general method.[1] In the case of aldehyde as a carbonyl group, yields of the direct cyclizations by silylacetylene and fluoride have been improved by us (addition of acetonitrile)[25] and Wender's group (addition of Ac_2O etc. as a trapping agent of the resulting alkoxide).[9c,26] Application of such improvements to methylketones such as **30**, however, have not given any better results.

In our previous paper (ref. 25), we did not clearly indicate the original reference for cyclization reported by Danishefsky *et al.* (ref. 23) and by Kende *et al.* (ref. 24), for which we apologize.



Scheme 5

Absolute stereochemistry of the final compound (+)-**28** was confirmed by conversion of the intermediate **26** into **31** illustrated in **Scheme 6**. Homologation of (–)-ketone **26** gave *tert*-alcohol **29**, of which semi-pinacol rearrangement[27] induced by $BF_3{\cdot}OEt_2$ gave methylketone **30**. The structure of **30** was confirmed by NMR and molecular mechanics calculations by using MacroModel (MM2 force field).[28] The stereostructure of rearranged product **30** suggested that this rearrangement occurred by first opening of epoxide to generate the benzyl cation and second migration of one of the methyls. The conformation of **30** is shown in **Figure 4**, in which the hydroxy group occupies *pseudo*-equatorial position. The absolute configuration of newly generated *sec*-alcohol in **30** was determined as *S* by modified Mosher's method[21] (**Figure 5**). Because *anti* relationship between acetylene and epoxide in **26** had been known, the absolute stereochemistry of (+)-**28** was proved as shown in **Scheme 5**.



Scheme 6

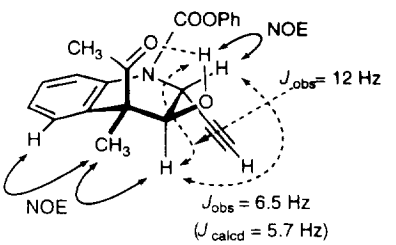


Figure 4. Conformation of 30

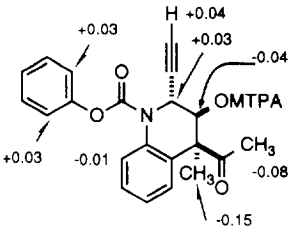
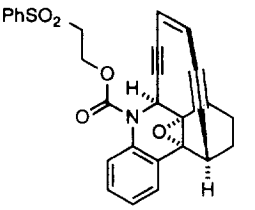


Figure 5. $\Delta\delta = \delta\,(S)\text{-}\delta\,(R)$



(+)-32

The absolute stereochemistry of (+)-**28** ($[\alpha]_D$ +530) is the same as the proposed absolute stereostructure of naturally occurring dynemicin A **1** ($[\alpha]_D$ +270)[2, 29] and that of Nicolaou's model **32** ($[\alpha]_D$ +586).[7]

Biological Activities

DNA-cleaving activities of the compounds synthesized above, were examined and compared. Incubation of supercoiled DNA (ΦX 174) with 1 mM each of (+)-**28** , (±)-**28** and (–)-**28** in phosphate buffer (pH 7.4) at 37 °C for 18 h caused DNA cleavage (form I → form II) as shown in **Figure 6**, which indicated that both enantiomers of **28** showed the almost same activity in this assay.

Compounds (+)-**28**, (±)-**28** and (–)-**28** inhibited the growth of human carcinoma KB cells in culture, giving IC_{50} values of 14, 5.7 and 3.9 μM, respectively. Compounds (–)-**28** exhibited higher potencies than (+)-**28**. This result is inconsistent with that of Nicolaou's model compound **32** in which (+)-enantiomer is more potent than (–)-enantiomer.[7] Compounds (±)-**28** showed good antitumor activity against murine P388 leukemia models, and which gave T/C of 131, 141 and 165 % at 0.5, 1, and 2 mg/kg, respectively (efficacy T/C >125 %).

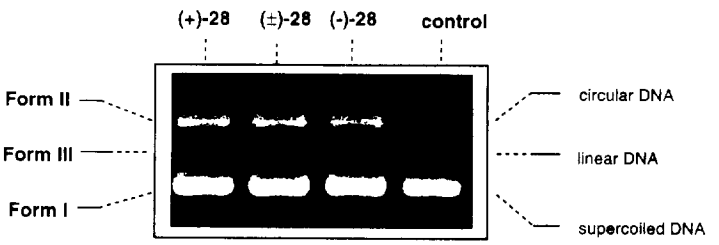


Figure 6. DNA cleaving activity

In summary, we have synthesized both enantiomers of dynemicin A model compound by means of a novel and highly selective asymmetric induction. This study provides a general method for asymmetric synthesis of dynemicin A and its analogs. On the other hand, studies on biological activities of the synthesized dynemicin A models suggested that these compounds may be good lead compounds for antineoplastic agent.[30]

Experimental Section[31]

Methoxymethyl ether 6: To a suspension of NaH (60% in mineral oil, 160 mg, 4.00 mmol, washed with hexane (x2)) in THF (4.0 mL) and DMF (4.0 mL) was added a solution of (±)-**5** (346 mg, 2.00 mmol) in DMF (2.0 mL). After stirred for 10 min, MOM-Cl (0.23 mL, 3.0 mmol) was added dropwise. The

mixture was stirred for 1 h, and quenched with aqueous NH_4Cl solution. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 19 g, ether/hexane = 3:1) to give (±)-**6** (276 mg, 65 %). IR (KBr) ν_{max} 2934, 1592, 1508 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.62 (3H, d, J = 7 Hz, CH_3-CH-Ar), 3.40 (3H, s, OCH_3), 4.61 (1H, d, J = 7 Hz, O-CH_AH_B-OMe), 4.72 (1H, d, J = 7 Hz, CH_AH_B-OMe), 5.51 (1H, d, J = 7 Hz, Me-CH-Ar), 7.54 (1H, d, J = 4.5 Hz, aromatic), 7.56 (1H, ddd, J = 8.5, 7, 1 Hz, aromatic), 7.71 (1H, ddd, J = 8.5, 7, 1 Hz, aromatic), 8.08 (1H, dd, J = 8, 1 Hz, aromatic), 8.15 (1H, dd, J = 8, 1 Hz, aromatic), 8.91 (1H, d, J = 4.5 Hz, N=CH). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 23.05, 55.53, 70.16, 94.59, 117.65, 123.08, 125.69, 126.41, 128.96, 130.31, 148.32, 149.10, 150.35. MS (EI) *m/z* 217 (M^+), 202. HRMS (EI) for $C_{13}H_{15}NO_2$ (M^+), calcd 217.1102, found 277.1097.

Methoxyethoxymethyl-ether 7: To a suspension of NaH (60% in mineral oil, 160 mg, 4.00 mmol, washed with hexane (x2)) in THF (4.0 mL) and DMF (4.0 mL) was added a solution of (±)-**5** (328 mg, 1.89 mmol) in DMF (2.0 mL). After stirred for 10 min, MEM-Cl (0.36 mL, 3.0 mmol) was added dropwise. The mixture was stirred for 1 h, and quenched with aqueous NH_4Cl solution. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 19 g, ether/hexane = 3:1) to give (±)-**7** (302 mg, 61 %). IR (KBr) ν_{max} 2933, 1592, 1508, 1027 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.66 (3H, d, J = 7 Hz, CH_3-CH-Ar), 3.35 (3H, s, CH_3-O), 3.50 (2H, m, OCH_2CH_2OMe), 3.58-3.70 (1H, m, $OCH_2CH_AH_B$-OMe), 3.80-3.88 (1H, m, $OCH_2CH_AH_B$-OMe), 4.69 (1H, d, J = 7 Hz, O-CH_CH_D-O), 4.85 (1H, d, J = 7 Hz, O-CH_CH_D-O), 5.55 (1H, q, J = 6 Hz, Me-CH-Ar), 7.52 (1H, d, J = 5 Hz, aromatic), 7.57 (1H, ddd, J = 8, 6.5, 1.5 Hz, aromatic), 7.71 (1H, ddd, J = 8, 6.5, 1.5 Hz, aromatic), 8.10 (1H, dd, J = 8, 1 Hz, aromatic), 8.15 (1H, dd, J = 8, 1 Hz, aromatic), 8.90 (1H, d, J = 5 Hz, N=CH). MS (EI) *m/z* 261 (M^+). HRMS (EI) for $C_{15}H_{19}NO_3$ (M^+), calcd 261.1364, found 261.1350.

***p*-Methoxybenzyl ether 8:** To a suspension of NaH (60% in mineral oil, 160 mg, 4.00 mmol, washed with hexane (x2)) in THF (4.0 mL) and DMF (4.0 mL) was added a solution of (±)-**5** (330 mg, 2.00 mmol) in DMF (1.0 mL). After stirred for 10 min, PMB-Cl (0.41 mL, 3.0 mmol) was added. The mixture was stirred at rt for 1 h, and quenched with aqueous NH_4Cl solution. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 35 g, ether/hexane = 2:1) to give (±)-**8** (474 mg, 85 %). IR (KBr) ν_{max} 2977, 1612, 1509, 1249 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.61 (3H, d, J = 7 Hz, CH_3-CH-Ar), 3.80 (3H, s, Ar-OCH_3), 4.32 (1H, d, J = 11 Hz, O-CH_AH_B-Ph-OMe), 4.48 (1H, d, J = 11 Hz, O-CH_AH_B-Ph-OMe), 5.22 (1H, q, J = 7 Hz, Me-CH-Ar), 6.88 (2H, d, J = 8.5 Hz, aromatic of PMB), 7.24 (2H, d, J = 8.5 Hz, aromatic of PMB), 7.57 (1H, d, J = 4.5 Hz, aromatic), 7.55 (1H, br t, J = 8 Hz, aromatic), 7.72 (1H, br t, J = 8 Hz, aromatic), 8.10 (1H, d, J = 8.5 Hz, aromatic), 8.17 (1H, d, J = 8.5 Hz, aromatic), 8.90 (1H, d, J = 4.5 Hz, N=CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.15, 55.09, 70.50, 73.34, 113.78, 117.83, 123.09, 125.97, 126.35, 128.96, 129.25, 130.01, 130.36, 148.47, 149.28, 150.43, 159.25. MS (EI) *m/z* 293 (M^+).

Benzoate 9: To a solution of (±)-**5** (509 mg, 2.89 mmol) in pyridine (15 mL) was added Bz-Cl (0.50 mL, 4.34 mmol). After stirred at rt for 14 h, small pieces of ice were added. The mixture was stirred for 30 min and extracted with AcOEt (x3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, diluted with toluene, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 48 g, ether/hexane = 2:1) to give (±)-**9** (863 mg, 100 %). IR (KBr) ν_{max} 3064, 1716, 1274 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.82 (3H, s, J = 6 Hz, CH_3-CH-Ar), 6.84 (1H, q, J = 6 Hz, CH_3-CH-Ar), 7.42-7.50 (2H, m, aromatic), 7.54-7.62 (2H, m, aromatic), 7.59 (1H, d, J = 4.5 Hz, aromatic), 7.74 (1H ddd, J = 8, 7, 1Hz, aromatic), 8.11-8.18 (3H, m, aromatic), 8.21 (1H, d, J = 8.0 Hz, aromatic), 8.95 (1H, d, J = 4.5 Hz, N=CH). MS (EI) *m/z* 277 (M^+). HRMS (EI) for $C_{18}H_{15}NO_2$ (M^+), calcd 277.1102, found 277.1089.

Triethylsilyl ether 10. A solution of the alcohol (±)-**5** (420 mg, 2.43 mmol) and imidazole (500 mg, 7.35 mmol), TES-Cl (0.61 mL, 3.63 mmol) in DMF (12.6 mL) was stirred at rt for 15 h. After cooling to 0 °C, the mixture was quenched with water (12 mL) and extracted with AcOEt (x3). The organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 18 g, ether/hexane = 1:2) to give (±)-**10** (440 mg, 63%). IR (KBr) ν_{max} 2956, 2875, 1593, 1507 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.55-0.66 (6H, m, $Si(CH_2CH_3)_3$), 0.93 (9H, t, J = 8 Hz, $Si(CH_2CH_3)_3$), 1.58 (3H, d, J = 6.5 Hz, CH_3-CH-Ar), 5.58 (1H. q, J = 6.5 Hz, CH_3-CH-OTES), 7.55 (1H, ddd, J = 8.5, 7, 1 Hz, aromatic), 7.63 (1H, d, J = 4.5 Hz, aromatic), 7.70 (1H, ddd, J = 8.5, 7, 1 Hz), 8.02 (1H, dd, J = 8.5, 1 Hz, aromatic), 8.15 (1H, dd, J = 8.5, 1

Hz, aromatic), 8.90 (1H, d, J = 4.5 Hz, N=C*H*). MS (EI) *m/z* 287 (M^+), 258. HRMS (EI) for $C_{17}H_{25}NOSi$ (M^+), calcd 287.1705, found 287.1969.

Typical experimental procedure for Table 1 (entry 2). To a cold solution of trimethylsilylacetylene (0.14 mL, 0.98 mmol) in dry THF (3 mL) was added dropwise a solution of EtMgBr (3M in Et_2O, 0.33 mL, 0.98 mmol) at 0 °C. The solution was stirred at rt for 30 min, and cooled to 0 °C again. To the solution was added a solution of **6** (102 mg, 0.47 mmol) in THF (1.0 mL) with stirring at 0 °C for 10 min. A solution of methyl chloroformate (0.09 mL, 1.20 mmol) was added. After stirring at 0 °C for 1 h, the reaction mixture was quenched with sat. NH_4Cl solution. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x3) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 9 g, ether/hexane = 1:0) to give 1,2-adduct **14** (114 mg, 65 %). The diastereomeric ratio of 1,2-adduct was determined by integration value of ^1H NMR (^1H NMR data estimated the diastereomeric ratio are described because of the complexity of diastereomeric mixture).

12: IR (KBr) ν_{max} 2958, 2171, 2093, 1751, 1717, 1440, 1265 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 6 Hz, C*H*$_3$-CH-Ar), 1.60 (d, J = 6 Hz, C*H*$_3$-CH-Ar). MS (EI) *m/z* 387 (M^+), 372.

13: IR (KBr) ν_{max} 2958, 2168, 1751, 1488, 1411, 1339, 1307 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.20 (9H, s, Si(C*H*$_3$)$_3$), 1.27 (3H, d, J = 6.5 Hz, C*H*$_3$CH-O), 3.67 (3H, s, OC*H*$_3$), 3.89 (3H, s, OC*H*$_3$), 4.88 (2H, q, J = 6.5 Hz, CH$_3$-C*H*-O), 5.28 (1H, d, J = 8 Hz, N-CH=C*H*), 7.12 (1H, d, J = 8 Hz, N-C*H*=CH), 7.21 (1H, td, J = 8, 1 Hz, aromatic), 7.31 (1H, td, J = 8.5, 1.5 Hz, aromatic), 7.65 (1H, dd, J = 8, 1.5 Hz, aromatic), 7.99 (1H, br d, J = 8.5 Hz, aromatic). MS (EI) *m/z* 387 (M^+), 372, 328. HRMS (EI) for $C_{20}H_{25}NO_5Si$ (M^+), calcd 387.1501, found 387.1492.

14: IR (KBr) ν_{max} 2958, 2170, 1712, 1601, 1488 cm^{-1}. MS (EI) *m/z* 373 (M^+), 358, 311, 284. ^1H NMR (270 MHz, $CDCl_3$) δ 1.36 (d, J = 7 Hz, C*H*$_3$-CH-Ar), 1.47 (d, J = 7 Hz, C*H*$_3$-CH-Ar).

15: IR (KBr) ν_{max} 2957, 2169, 1707, 1601, 1571, 1491 cm^{-1}. MS (EI) *m/z* 402 (M-15), 358, 321. ^1H NMR (270 MHz, $CDCl_3$) δ 1.35 (d, J = 7 Hz, C*H*$_3$-CH-Ar):1.45 (d, J = 7 Hz, C*H*$_3$-CH-Ar).

16: IR (KBr) ν_{max}.2957, 2169, 1710, 1612, 1513, 1440, 1377, 1250 cm^{-1}. MS (EI) *m/z* 449 (M^+). ^1H NMR (270 MHz, $CDCl_3$) δ 1.46 (d, J = 6.5 Hz, C*H*$_3$-CH-Ar), 1.37 (d, J = 6.5 Hz, C*H*$_3$-CH-Ar), 6.04 (dd, J = 6.5 Hz, olefinic), 6.19 (dd, J = 6.5, 1 Hz, olefinic).

17: IR (KBr) ν_{max} 2957, 2168, 1706, 1489, 1438, 1379 cm^{-1}. MS (EI) *m/z* 433 (M^+). ^1H NMR (270 MHz, $CDCl_3$) δ 8.01 (dt, J = 9, 2 Hz, aromatic), 8.12 (dt, J = 9, 2 Hz, aromatic).

18: IR (KBr) ν_{max} 2957, 2876, 2170, 1710, 1488 cm^{-1}. MS (EI) *m/z* 443 (M^+), 428, 414, 384. ^1H NMR (270 MHz, $CDCl_3$) δ 4.65 (q, J = 6 Hz, Me-C*H*-Ar) : 4.95 (qd, J = 6, 1.5 Hz, Me-C*H*-Ar).

19: IR (KBr) ν_{max} 2959, 2170, 1713, 1114 cm^{-1}. MS (EI) *m/z* 567 (M^+). ^1H NMR (270 MHz, $CDCl_3$) δ 4.58 (q, J = 6 Hz, CH$_3$-C*H*-Ar), 4.94 (qd, J = 6, 1 Hz, CH$_3$-C*H*-Ar).

20: IR (KBr) ν_{max} 2959, 2168, 1709, 1489, 1390, 1261 cm^{-1}. MS (EI) *m/z* 643 (M^+), 586, 552, 542, 508. ^1H NMR (270 MHz, $CDCl_3$) δ 4.58 (q, J = 6.5 Hz, CH$_3$-C*H*-Ar), 4.93 (qd, J = 6.5, 1 Hz, CH$_3$-C*H*-Ar).

21: ^1H NMR (270 MHz, $CDCl_3$) δ 5.85 (d, J = 7 Hz, olefinic), 6.48 (dd, J = 6.5, 1 Hz, olefinic).

23: IR (KBr) ν_{max} 2957, 2170, 1716, 1514, 1378 cm^{-1}. MS (EI) *m/z* 511 (M^+), 434. ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (d, J = 6.5 Hz, olefinic), 6.26 (dd, J = 6.5, 0.5 Hz, olefinic).

Resolution of racemic alcohol 5. The (±)-alcohol **5** (10.0 g, 57.7 mmol) was dissolved in dry THF (80 mL) and vinyl acetate (freshly distilled, 27 mL, 290 mmol). To this mixture was added lipase **LIP** (2.00 g) and the mixture was stirred at rt overnight. The lipase (2.0 g) was added each day until a total of 10 g had been added to the reaction mixture. After stirring overnight, the mixture was filtered through a pad of Super-Cel®, washed with AcOEt. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica 350g, ether/hexane = 4:1) to give acetate **(+)-24** (6.28 g, 51 %) and alcohol **(–)-5** (4.78 g, 48 %, 95 %ee by ^1H NMR analysis of its (*R*)-MTPA ester). **(+)-Acetate 24.** $[\alpha]_D$ +39.0° (*c* 1.00, $CHCl_3$). IR (KBr) ν_{max} 2992, 1742, 1236 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.68 (3H, d, J = 8 Hz, C*H*$_3$-CH), 2.17 (3H, s, C*H*$_3$CO), 6.60 (1H, q, J = 8 Hz, CH$_3$-C*H*), 7.47 (1H, d, J = 5.5 Hz, aromatic), 7.60 (1H, dd, J = 11, 8.5, 1.5 Hz, aromatic), 8.05 (1H, br d, J = 11 Hz, aromatic), 8.15 (1H, dd, J = 11, 1 Hz, aromatic), 8.91 (1H, br d, J = 5.5 Hz, N=C*H*). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 21.1, 21.7, 68.2, 117.1, 122.8, 125.0, 126.8, 129.2, 130.4, 147.1, 148.3, 150.2, 169.9. MS (EI) *m/z* 215 (M^+). HRMS (EI) for $C_{13}H_{13}NO_2$ (M^+), calcd 215.0946, found 215.0938. **(–)-Alcohol 5**. $[\alpha]_D$ -86.6° (*c* 1.00, $CHCl_3$). IR (KBr)

ν_{max} 3215, 2975, 1592, 1511, 1121, 1070 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.64 (3H, d, J = 6.5 Hz, CH_3-CH), 3.32 (1H, br s, CH-O*H*), 5.65 (1H, q, J = 6.5 Hz, CH-CH_3), 7.53 (1H, ddd, J = 8.5, 7, 1.5 Hz, aromatic), 7.57 (1H, d, J = 4.5 Hz, aromatic), 7.67 (1H, ddd, J = 8.5, 7, 1.5 Hz, aromatic), 8.01 (1H, dd, J = 8, 1.5 Hz, aromatic), 8.08 (1H, dd, J = 8, 1.5 Hz, aromatic), 8.76 (1H, d, J = 4.5 Hz, N=C*H*). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 24.6, 65.9, 116.7, 123.0, 125.3, 126.5, 129.1, 129.9, 147.9, 150.3, 151.7. MS (EI) *m/z* 173 (M^+). HRMS (EI) for $C_{11}H_{11}NO$ (M^+), calcd 173.0840, found 173.0834. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.26; H, 6.40; N, 8.09. Found C, 76.49; H, 6.28; N, 7.80.

(+)-Alcohol 5. The acetate **(+)-24** (1.01 g, 4.68 mmol) was dissolved in MeOH (30 mL). To this solution was added K_2CO_3 (600 mg). After stirring at rt for 2 h, the mixture was evaporated. The residue was dissolved in CH_2Cl_2-water, extracted with CH_2Cl_2 (x2). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography (silica 40 g, CH_2Cl_2/MeOH = 20:1) to give alcohol **(+)-5** (770 mg, 95 %, 96 % ee by ^1H NMR analysis of its (*R*)-MTPA ester). $[\alpha]_D$ +84.4° (*c* 1.19, $CHCl_3$). The ^1H NMR and MS spectra were identical with those of **(–)-5**.

***(R)*-MTPA ester of (+)-5.** To a solution of the alcohol **(+)-5** (10 mg, 0.058 mmol) in CH_2Cl_2 (0.2 mL) were added DMAP (7.1 mg, 0.058 mmol), Et_3N (38 μL, 0.28 mmol), and (*S*)-MTPA-Cl (16 mL, 0.087 mmol). After stirring at rt for 15 min, the mixture was quenched with 3-(dimethylamino)propylamine (20 mL, 0.16 mmol) and concentrated under reduced pressure. The residue was purified by TLC (ether) to give the (*R*)-MTPA ester (20 mg, 89%). IR (KBr) ν_{max} 2951, 1747, 1595, 1511, 1451 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.72 (3H, d, J = 6 Hz, CH_3-CH), 3.49 (3H, br q, J = 1 Hz, CH_3O), 6.84 (3H, br q, J = 6 Hz, CH-OMTPA), 7.32-7.53 (5H, m, aromatic of MTPA), 7.42 (1H, d, J = 4.5 Hz, 3-H), 7.60 (1H, ddd, J = 8, 7, 1 Hz, H-6), 7.75 (1H, m, J = 8, 7, 1 Hz, H-7), 8.02 (1H, br d, J = 8 Hz, H-5), 8.17 (1H, br d, J = 8 Hz, H-8), 8.89 (1H, d, J = 4.5 Hz, H-2). MS (EI) *m/z* 389, 189, 156. HRMS (EI) for $C_{21}H_{18}NO_3F_3$ (M^+), calcd 389.1238, found 389.1220.

***(S)*-MTPA ester of (+)-5.** Prepared in 85% from **(+)-5** in a similar manner to that described for (*R*)-MTPA ester of **(+)-5** IR (KBr) ν_{max} 2988, 1752, 1595, 1508, 1451 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.78 (3H, d, J = 6.5 Hz, CH_3-CH), 3.62 (3H, br q, J = 1 Hz, CH_3 of MTPA), 6.80 (1H, q, J = 7 Hz, CH-OMTPA), 7.18 (1H, d, J = 5 Hz, H-3), 7.31-7.50 (5H, aromatic of MTPA), 7.56 (ddd, J = 8, 7, 1 Hz, H-6), 7.73 (1H, ddd, J = 8, 7, 1 Hz, H-7), 7.97 (1H, br d, J = 8 Hz, H-5), 8.15 (1H, br d, J = 8 Hz, H-8), 8.79 (1H, d, J = 5 Hz, H-1). MS (EI) *m/z* 389, 189, 156. HRMS (EI) for $C_{21}H_{18}NO_3F_3$ (M^+), calcd 389.1238, found 389.1226.

Mitsunobu Inversion: (1) The alcohol **(+)-5** (100 mg, 0.58 mmol, 96 % ee) was dissolved in THF (2.5 mL). To this solution were added Ph_3P (302 mg, 1.20 mmol) and benzoic acid (140 mg, 1.20 mmol) and the mixture was cooled to 0 °C. DEAD (0.2 mL, 1.2 mmol) was added, and the mixture was allowed to warm to rt. After stirring at rt for 1 h, the mixture was evaporated. The residue was dissolved in ether, and the solution was washed with sat. $NaHCO_3$ solution (x3), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 25g, ether/hexane = 3:1) and then preparative TLC (silica, AcOEt/hexane = 3:1) to give the benzoate (124 mg, 77 %). ^1H NMR (270 MHz, $CDCl_3$) δ 1.83 (3H, d, J = 6.5 Hz, CH_3), 6.84 (1H, q, J = 6.5 Hz, CH-OBz), 7.44-7.78 (6H, m, aromatic), 8.10-8.20 (4H, m, aromatic), 8.92 (1H, d, J = 4H, aromatic). (2) The benzoate (23 mg, 0.083 mmol) was dissolved in MeOH (1.2 mL). After cooling to 0 °C, a solution of MeONa (2M solution in MeOH, 0.04 mL, 0.083 mmol) was added. After stirring at 0 °C for 1 h 10 min, the solution was stirred at rt for 25 min. The mixture was mixed with water, extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by preparative TLC to give **(–)-5** (13 mg, 90 %, 96 % ee by ^1H NMR analysis of its (*R*)-MTPA ester).

(–)-*t*-Butyldiphenylsilyl ether 11. A solution of **(–)-5** (4.61 g, 26.6 mmol), imidazole (5.50g, 80.8 mmol) and TBDPS-Cl (8.40 mL, 32.3 mmol) was stirred at 70 °C for 19 h. After cooling to 0 °C, the mixture was quenched with sat. $NaHCO_3$ solution, extracted with ether (x4). The combined organic layer was washed with brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 300 g, ether/hexane = 1:3) to give **(–)-11** (10.2 g, 92 %). $[\alpha]_D$ -50.6° (*c* 0.810, $CHCl_3$). IR (KBr) ν_{max} 3072, 2933, 2858, 1592, 1510, 1472, 1428 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.12 (9H, s, $SiC(CH_3)_3$), 1.48 (3H, d, J = 6 Hz, CH-CH_3), 5.55 (1H, q, J = 6 Hz, CH_3-CH), 7.18 (2H, tt, J = 7, 1.5 Hz, aromatic), 7.30 (1H, tt, J = 7, 1.5 Hz, aromatic), 7.36-7.50 (6H, m, aromatic), 7.61-7.67 (1H, m, aromatic), 7.67 (1H, d, J = 5 Hz, aromatic), 7.73-7.78 (2H, m, aromatic), 7.80 (1H, br d, J = 8 Hz, aromatic), 8.11 (1H, br d, J = 8 Hz, aromatic), 8.90 (1H, d, J = 5 Hz, CH=N). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 19.2, 26.0, 26.8, 68.2, 117.4, 123.0, 124.9, 126.0, 127.4, 127.6, 128.7, 129.6, 129.7,

130.1, 132.9, 133.7, 135.5, 135.7, 148.1, 150.4, 151.6. MS (EI) *m/z* 354 (M-C_6H_5). Anal. Calcd for $C_{27}H_{31}ONSi$: C, 78.79; H, 7.10; N, 3.40. Found C, 78.82; H, 7.00; N, 3.38.

(+)- 11. Prepared in 86 % from **(+)-5** in a similar manner to that described for **(–)-11**. $[\alpha]_D$ +51.3° (c 1.07, $CHCl_3$). The ^1H NMR and MS spectra were identical with those of **(–)-11**.

(+)-Phenyl carbamate 21. To a cold solution of trimethylsilylacetylene (3.6 mL, 26 mmol) in dry THF (56 mL) was added dropwise EtMgBr (3M in Et_2O, 8.6 mL, 26 mmol) at 0 °C. The solution was stirred at rt for 30 min, and cooled to -78 °C again. To the resultant solution was added a solution of **(–)-25** (7.05 g, 17 mmol) in THF (28 mL) *via* a cannula tubing. After stirring at -78 °C for 2 h 10 min, a solution of phenyl chloroformate (4.3 mL, 34 mmol) in THF (21 mL) cooled to -78 °C was added *via* a cannula tubing. After stirring at -78 °C for further 2 h 35 min, the reaction mixture was quenched with sat. NH_4Cl solution. The mixture was extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 400 g, ether/hexane = 1:15) to give **(+)-21** (7.68 g, 71 %). $[\alpha]_D$ +155° (*c* 1.08, $CHCl_3$). IR (KBr) ν_{max} 3072, 2962, 2856, 2171, 1783, 1720, 1593, 1488 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.06 (9H, s, $Si(CH_3)_3$), 1.06 (9H, s, $SiC(CH_3)_3$), 1.43 (3H, d, *J* = 6.5 Hz, CH_3-CH), 4.63 (1H, q, *J* = 6.5 Hz, C*H*-OTBDOS), 5.78 (1H, d, *J* = 7 Hz, olefinic, or propargylic), 5.85 (1H, d, *J* = 7 Hz, olefinic, or propargylic), 7.12-7.46 (14H, m, aromatic), 7.63-7.78 (2H, m, aromatic), 7.72-7.77 (2H, m, aromatic), 7.86 (1H, dd, *J* = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.2, 19.3, 23.8, 27.0, 44.8, 71.6, 88.7, 101.0, 121.6, 124.6, 125.0, 125.7, 127.4, 127.6, 129.3, 129.6, 129.7, 133.2, 134.2, 135.8, 136.2, 138.4, 151.0. MS (EI) *m/z* 629 (M^+). Anal. Calcd for $C_{39}H_{43}O_3NSi_2$: C, 74.36; H, 6.89; N, 2.22. Found C, 74.41; H, 6.80; N, 2.23.

(–)- 21. Prepared in 68 % from **(+)-11** in a similar manner to that described for **(+)-21**. $[\alpha]_D$ -163° (c 1.02, $CHCl_3$). The ^1H NMR and MS spectra were identical with those of **(+)-21**.

(+)-Allyl alcohol 22. The silylacetylene **(+)-21** (1.99 g, 3.15 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. To this solution were added MeOH (0.26 mL, 6.30 mmol) and *n*-Bu_4NF (1 M in THF, 1.6 mL, 1.6 mmol). After stirring at -78 °C for 25 min, the reaction mixture was quenched with sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The crude product was dissolved in MeOH (40 mL) and mixed with TsOH·H_2O (1.27 g, 6.68 mmol). The mixture was heated at reflux for 11.5 h. After cooling to rt, pyridine (1.1 mL, 13.4 mmol) was added and the mixture was concentrated under reduced pressure. The residue was dissolved in AcOEt and the organic layer was washed with water (x2), sat. NH_4Cl solution (x1) and brine (x2), dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was purified by column chromatography (silica 80 g, ether/hexane = 3:2) to give **(+)-22** (850 mg, 84 % 2 steps). $[\alpha]_D$ +316° (*c* 0.434, $CHCl_3$). IR (KBr) ν_{max} 3442, 3290, 2974, 2112, 1713, 1592, 1489 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ . 1.56 (3H, d, *J* = 6 Hz, CH_3-CH), 1.87 (1H, d, *J* = 4 Hz, O*H*), 2.23 (1H, d, *J* = 3 Hz, C≡C-*H*), 4.91 (1H, m, CH_3-C*H*), 6.00 (1H, dd, *J* = 6, 3 Hz, propargylic), 6.18 (1H, dd, *J* = 6, 1 Hz, olefinic), 7.15-7.42 (7H, m, aromatic), 7.60 (1H, dd, *J* = 8, 2 Hz, aromatic), 7.76 (1H, d, *J* = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 21.9, 43.9, 66.8, 72.1, 79.6, 121.5, 124.0, 124.9, 125.1, 125.8, 128.1, 129.4, 139.2, 150.8. MS (EI) *m/z* 319 (M^+), 275, 242. HRMS (EI) for $C_{20}H_{17}NO_3$ (M^+), calcd 319.1208, found 319.1218.

(–)-22. Prepared in 84 % from **(–)-21** in a similar manner to that described for **(+)-22**. $[\alpha]_D$ -336° (c 0.957, $CHCl_3$). The ^1H NMR and MS spectra were identical with those of **(+)-22**.

(+)-Epoxy alcohol 25. The (+)-allylic alcohol **22** (829 mg, 2.60 mmol) and Na_2HPO_4 (1.55 g, 8.82 mmol) were dissolved in CH_2Cl_2 (25 mL) and the mixture was cooled to 0 °C. To this solution was added MCPBA (ca. 80 % purity, 952 mg, 4.41 mmol) portionwise. After stirring at 0 °C for 2 h 10 min, additional MCPBA (80 % purity, 112 mg, 0.52 mmol) was added. The mixture was stirred at 0 °C for 1 h and quenched by a portionwise addition of Na_2SO_3 until KI starch paper became negative. The aqueous layer was extracted with CH_2Cl_2 (x2). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica 45 g, ether/hexane = 3:1) to give **(+)-25** (776 mg, 89 %). $[\alpha]_D$ +142° (*c* 1.01, $CHCl_3$). IR (KBr) ν_{max} 3514, 3284, 2981, 2121, 1721, 1593, 1495 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.44 (3H, d, *J* = 6 Hz, CH_3-CH), 1.58 (1H, s, O*H*), 2.23 (1H, d, *J* = 2.5 Hz, C≡C-*H*), 4.09 (1H, d, *J* = 3 Hz, epoxide), 4.84 (1H, br q, *J* = 6 Hz, C*H*-OH), 5.94 (1H, t, *J* = 2 Hz, C*H*-C≡C), 7.13 (2H, d, *J* = 7 Hz, aromatic), 7.18-7.30 (2H, m, aromatic), 7.32-7.43 (3H, m, aromatic), 7.54 (1H, dd, *J* = 8 Hz, aromatic), 7.60 (1H, br d, *J* = 8 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 19.3, 43.4, 58.8, 61.5, 62.2, 74.2, 77.1, 121.4, 124.9, 125.6, 125.7, 126.7, 127.2, 128.7, 129.3, 135.0, 150.8. MS (EI) *m/z* 335 (M^+). HRMS (EI) for $C_{20}H_{17}NO_4$ (M^+), calcd 335.1157, found 335.1142.

(–)-25. Prepared in 99 % from **(–)-22** in a similar manner to that described for **(+)-25**. $[\alpha]_D$ -127° (*c* 1.18, $CHCl_3$). The ^1H NMR and MS spectra were identical with those of **(+)-25**.

(+)-Epoxyketone 26. The (+)-epoxyalcohol **25** (768 mg, 2.29 mmol) was dissolved in CH_2Cl_2 (6 mL), DMSO (12 mL) and Et_3N (4.8 mL, 34 mmol), and the mixture was cooled to 0 °C. To this solution was added SO_3·Py (3.64 g, 22.9 mmol) portionwise. After stirring at rt for 1.5 h, the mixture was quenched with sat. NH_4Cl solution, extracted with AcOEt (x3). The combined organic layer was washed with brine (x3), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography (silica 40 g, ether/hexane = 1:1) to give **(+)-26** (593 mg, 78 %). $[\alpha]_D$ +123° (*c* 0.957, $CHCl_3$). IR (KBr) ν_{max} 3289, 3073, 2123, 1720, 1493 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 2.27 (1H, d, *J* = 2 Hz, C≡C-*H*), 2.37 (3H, s, CH_3CO), 4.04 (1H, d, *J* = 3 Hz, epoxide), 5.99 (1H, dd, *J* = 3 Hz, C≡C-C*H*), 7.13 (2H, br d, *J* = 8 Hz, aromatic), 7.26 (2H, tt, *J* = 8, 1 Hz, aromatic), 7.32-7.45 (3H, m, aromatic), 7.58 (1H, br d, *J* = 8 Hz, aromatic), 7.69 (1H, dd, *J* = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 26.5, 43.2, 59.9, 64.5, 75.0, 76.0, 121.3, 122.1, 125.8, 127.2, 128.7, 129.2, 129.3, 134.6, 150.8. MS (EI) *m/z* 333 (M^+). Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found C, 72.02; H, 4.49; N, 4.17.

(–)-26. Prepared in 75 % from **(–)-25** in a similar manner to that described for **(+)-26.** $[\alpha]_D$ -120° (*c* 1.08, $CHCl_3$). The ^1H NMR, and MS spectra were identical with those of **(+)-26**.

(+)-Enediyne 27. A suspension of (+)-**26** (203 mg, 0.609 mmol), $Pd_2[dba]_3$·$CHCl_3$ (15.5 mg, 0.152 mmol), Ph_3P (16 mg, 0.061 mmol) and CuI (11.6 mg, 0.061 mmol) in benzene (7.5 mL) was degassed by three freeze-thaw cycles and covered with argon. To this mixture were added (*Z*)-chloro-4-trimethylsilyl-1-buten-3-yne (80 % purity, 456 mg, 2.44 mmol) in benzene (1.5 mL) and *n*-$BuNH_2$ (0.12 mL, 1.22 mmol). After stirring at rt for 2 h under argon, the mixture was quenched with sat. NH_4Cl solution, and extracted with AcOEt (x3). The combined organic layer was washed with brine, died over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 25 g, ether/hexane = 1:3) to give (+)-**27** (176 mg, 64 %). $[\alpha]_D$ +92.2° (*c* 0.434, $CHCl_3$). IR (KBr) ν_{max} 3049, 2967, 2142, 1716, 1582, 1492 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 0.23 (9H, s, $Si(CH_3)_3$), 2.37 (3H, s, CH_3CO), 4.07 (1H, d, *J* = 2.5 Hz, epoxide), 5.69 (1H, dd, *J* = 11, 2 Hz, C*H*=CH-C≡C-TMS), 5.84 (1H, d, *J* = 11 Hz, CH=C*H*-C≡C-TMS), 6.24 (1H, t, *J* = 2.5 Hz, C*H*-C≡C), 7.14 (2H, d, *J* = 8 Hz, aromatic), 7.19-7.29 (2H, m, aromatic), 7.33-7.44 (3H, m, aromatic), 7.59 (1H, br d, *J* = 8 Hz, aromatic), 7.71 (1H, dd, *J* = 8, 1 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ -0.1, 26.5, 44.1, 59.9, 64.5, 83.3, 88.7, 101.3, 103.8, 118.9, 121.1, 121.3, 122.1, 125.8, 127.2, 128.7, 129.1, 129.3, 134.6, 150.6, 202.5. MS (EI) *m/z* 456 (M^+). Anal. Calcd for $C_{27}H_{25}O_4NSi$: C, 71.18; H, 5.53; N, 3.07. Found C, 71.21; H, 5.49; N, 3.07.

(–)-27. Prepared in 57 % from **(–)-26** in a similar manner to that described for **(+)-27**. $[\alpha]_D$ -76.0° (*c* 0.570, benzene). The ^1H NMR and MS spectra were identical with those of **(+)-27**.

(+)-Model compound 28. A CsF powder (67 mg, 0.44 mmol) was placed in a dry two necked flask and heated at 100 °C *in vacuo* for 1 h 50 min. After cooling to rt, dry THF (20 mL) was added. To this suspension were added **(+)-27** (115 mg, 0.253 mmol) in THF (2.5 mL) and 18-crown-6 (100 mg, 0.379 mmol) in THF (1.0 mL). After stirring at rt for 4 h, the reaction was quenched with sat. NH_4Cl solution, and extracted with AcOEt (x3). The combined organic layer was washed with water (x2) and brine (x2), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2) to give (+)-**28** (10.8 mg, 12 %). $[\alpha]_D$ +530° (*c* 0.54, benzene). IR (KBr) ν_{max} 3469, 3060, 1720, 1492, 1381, 1324, 1204 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.73 (3H, s, $C(OH)CH_3$), 4.07 (1H, d, *J* = 3 Hz, epoxide), 5.67 (1H, dd, *J* = 10, 2 Hz, N-CH-C≡C-C*H*=CH), 5.82 (1H, d, *J* = 10 Hz, N-CH-C≡C-CH=C*H*), 5.89 (1H, dd, *J* = 3, 2 Hz, propargylic), 7.14 (2H, br d, J = 8 Hz, aromatic), 7.20-7.28 (2H, m, aromatic), 7.31-7.41 (3H, m, aromatic), 7.51 (1H, br d, *J* = 8 Hz, aromatic), 8.80 (1H, dd, *J* = 8, 1.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 25.33, 45.82, 61.96, 65.81, 72.37, 88.94, 90.58, 92.43, 102.05, 121.50, 122.09, 124.66, 125.59, 125.75, 126.66, 127.12, 128.31, 129.36, 131.74, 135.32, 151.00. MS (EI) *m/z* 383 (M^+). HRMS (EI) for $C_{24}H_{17}O_4N$ (M^+), 383.1157, found 383.1156.

(–)-28. Prepared in 12 % from **(–)-27** in a similar manner to that described for **(+)-28.** $[\alpha]_D$ -591° (*c* 0.50, benzene). The ^1H NMR and MS spectra were identical with those of **(+)-28**.

(–)-*t*-Alcohol 29. The epoxyketone **(–)-26** (166 mg, 0.498 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. To this solution was added a solution of MeMgBr (0.9 M in THF, 0.83 mL, 0.75 mmol). After stirring at 0 °C for 20 min, the mixture was quenched with sat. NH_4Cl solution, and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica 10 g, ether/hexane = 1:1) to give **(–)-29** (175 mg, quant). $[\alpha]_D$ -171° (*c* 1.39, $CHCl_3$). IR (KBr) ν_{max} 3468, 3290, 2979, 2121, 1717, 1492, 1378, 1327, 1205 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.54 (3H, s, CH_3-C-OH), 1.70 (3H, s, CH_3-C-OH), 2.20 (1H, d, *J* = 2.5 Hz, C≡C-*H*), 4.21 (1H, d, *J* = 3 Hz, epoxide), 5.86 (1H, t, *J* = 3 Hz, C≡C-C*H*), 7.09-7.41 (7H, m, aromatic), 7.56 (1H, br d, *J* = 8 Hz, aromatic), 8.05 (1H, br d, *J* = 8 HZ, aromatic). ^{13}C

NMR (67.9 MHz, $CDCl_3$) δ 25.9, 27.5, 43.5, 61.6, 63.8, 70.6, 74.1, 77.2, 121.4, 125.3, 125.5, 125.6, 127.8, 129.2, 129.6, 135.7, 150.9. MS (EI) *m/z* 349 (M^+). HRMS (EI) for $C_{21}H_{19}NO_4$ (M^+), calcd 349.1313, found 349.1300.

(–)-Methyl ketone 30. The alcohol **(–)-29** (32 mg, 0.092 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to -78 °C. To this solution was added $BF_3{\cdot}OEt_2$ (0.45 M in CH_2Cl_2, 0.10 mL, 0.046 mmol). After stirring for 35 min, the reaction mixture was allowed to warm to -20 °C and stirred for 1 h. The mixture was quenched with sat. $NaHCO_3$ solution, and extracted with CH_2Cl_2 (x3). The combined organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (ether/hexane = 2:1, CH_2Cl_2) to give **(–)-30** (16.8 mg, 52 %). $[\alpha]_D$ -222° (*c* 0.28, $CHCl_3$). IR (KBr) ν_{max} 3490, 3289, 2929, 2121, 1728, 1489, 1375, 1321, 1201 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.75 (3H, s, Ar-C-C*H*$_3$), 1.83 (3H, s, C*H*$_3$-CO), 2.33 (1H, d, *J* = 2Hz, C≡C-*H*), 3.61 (1H, dd, *J* = 12, 7 Hz, C*H*-OH), 4.24 (1H, d, *J* = 12 Hz, O*H*), 5.10 (1H, br d, *J* = 7 Hz, C≡C-C*H*), 7.15 (2H, br d, *J* = 8 Hz, aromatic of PhO), 7.23 (1H, br t, *J* = 7.5 Hz, aromatic), 7.32-7.48 (5H, m, aromatic), 7.62 (1H, br d, *J* = 7.5 Hz, aromatic). ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 17.6, 26.7, 53.0, 54.2, 71.6, 82.3, 83.2, 121.4, 124.8, 125.8, 126.3, 126.9, 128.7, 129.3, 133.9, 135.5, 150.8, 152.0, 214.9. MS (EI) *m/z* 306 (M-C_2H_3O), 289 (306-OH). MS (FAB) *m/z* 350 (M+H). HRMS (FAB) for $C_{21}H_{20}NO_4$ (M+H), calcd 350.1392, found 350.1379.

(*S*)-MTPA ester 31. Prepared in 64% from **(–)-30** in a similar manner to that described for (*R*)-MTPA ester of **(+)-5**. IR (KBr) ν_{max} 3276, 2955, 2121, 1731 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.53 (3H, s, C*H*$_3$-C-Ar), 1.79 (3H, s, C*H*$_3$-CO), 2.37 (1H, d, *J* = 2.5 Hz, C≡C-*H*), 3.61 (3H, br s, C*H*$_3$O), 5.31 (1H, d, *J* = 7 Hz, C*H*-OMTPA), 5.58 (1H, br d, *J* = 7 Hz, C≡C-C*H*), 7.16 (2H, *J* = 18 Hz, aromatic of PhO), 7.23 (1H, br t, *J* = 8 Hz, aromatic), 7.30-7.47 (8H, m, aromatic), 7.63 (2H, m, aromatic of MTPA), 7.66 (1H, br d, *J* = 7.5 Hz, aromatic). MS (EI) *m/z* 565 (M^+), 522. HRMS (EI) for $C_{31}H_{26}NO_6F_3$ (M^+), calcd 565.1712, found 565.1698.

(*R*)-MTPA ester 31. Prepared in 68% from **(–)-30** in a similar manner to that described for (*R*)-MTPA ester of **(+)-5**. IR (KBr) ν_{max} 3289, 2950, 2123, 1734 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 1.68 (3H, s, C*H*$_3$-C-Ar), 1.87 (3H, s, C*H*$_3$CO), 2.33 (1H, d, *J* = 2.5 Hz, C≡C-*H*), 3.56 (3H, br s, C*H*$_3$O), 5.35 (1H, d, *J* = 7 Hz, C*H*-OMTPA), 5.55 (1H, dd, *J* = 7, 2.5 Hz, C≡C-C*H*), 7.13 (2H, *J* = 8 Hz, aromatic of PhO), 7.22 (1H, br t, *J* = 7.5 Hz, aromatic), 7.31-7.47 (8H, m, aromatic), 7.8 (2H, m, aromatic of MTPA), 7.67 (1H, br d, *J* = 8 Hz, aromatic). MS (EI) *m/z* 565 (M^+), 522. HRMS (EI) for $C_{31}H_{26}NO_6F_3$ (M^+), calcd 565.1712, found 565.1702.

DNA-cleaving assay of compounds (+)-**28**, (±)-**28**, (–)-**28.** Supercoiled ΦX174 DNA (90 % form I, 250 μM/bp) was incubated with 1mM (final concentration) of an given enediyne compound in a buffer solution (50 mM phosphate buffer, pH 7.4) at 37 °C for 18 h and analyzed by agarose gel electrophoresis to separate the various forms of DNA. The DNA bands were visualized with ethidium bromide binding and UV illumination

***In vitro* Cytotoxicity.** Human epidermoid carcinoma KB cells were cultured with Eagle's minimum essential medium containing 10 % fetal bovine serum at a density of 5×10^4 cells/mL on day 0. After culture with a test sample for 48 h from day 1 to day 3, the number of living cells was counted with a Coulter counter on day 3.

P388 leukemia *in vivo* assay. CDF_1 Mice were injected i.p. with 1×10^6 cells/mouse of P388 on day 0 and were treated i.p. with (±)-**28** once daily for 4 days from day 1 to 4. Survival was recorded for 30 days. The T/C values reported refer the relative median survival times of drug-treated and control mice, ×100 (and expressed as a percentage).

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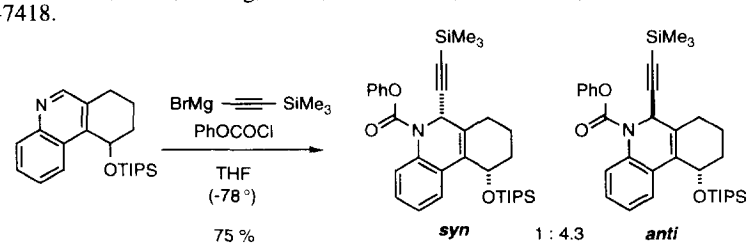

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