—Articles—

Synthetic Study of 4-Aza-4-deoxypodophyllotoxins

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The diastereoselective Michael addition of aryllithium to novel quinolines bearing oxazolines as chiral auxiliary was examined for the possible synthesis of the chiral antitumor compound 4-aza-4-deoxypodophyllotoxin (PDX). Unfortunately, most of our trials resulted affording undesired product formed by oxazoline ring opening with aromatization of C-ring in the 4-aza-4-deoxyPDX skeleton. Only successfully obtained Michael adduct, which had a methyl group at C-3, was also aromatized to 4-aza-1,2,3,4-tetradehydro-4-deoxyPDX during transformation to the target molecule.

Key words——synthesis; antitumor; 4-aza-4-deoxypodophyllotoxin; chiral oxazoline; aromatization

INTRODUCTION

Because of their strong antifungal or anticancer activity, a number of studies on the isolation or synthesis of lignans, which are compounds consisting of two phenylpropanoid molecules, have been conducted.[1-7] We have been engaged in the isolation and synthesis of cytotoxic lignans from Okinawan *Hernandia ovigera* L. since 1976.[7-15]

The most popular lignan is podophyllotoxin (PDX) (**1**), the major compound in *Podophyllum* sp. However, PDX **1** could not be used as a drug because of its excessive toxicity.[1] After natural PDX was chemically modified, it was developed into clinical anticancer drugs etoposide (**2**) and teniposide (**3**), as shown in Fig. 1.[16,17] Interestingly, the anticancer activity of **2** and **3** is due to DNA topoisomerase II inhibition, whereas the cytotoxicity of mother compound **1** is effected by inhibiting tubulin formation. Another promising candidate for phase II clinical trial is GL-331 (**4**).[18] Clearly, the synthesis of PDX analogues is important for new drug discovery. Recent synthetic targets receiving great attention are azapodophyllotoxins (azaPDXs) (**5**–**7**) since of the potential as new anticancer drug candidates.[19-35] Compound **5** had almost same cytotoxicity against P388 leukemia cells as **1**.[30] And compound **6** was elucidated to be extremely cytotoxic on various tumor cell lines by inhibition of microtubule assembly like **1**.[35] Therefore we are also interested in the chiral synthesis of azapodophyllotoxins.[29]

In 1999, Takeya and co-workers reported the successful synthesis of chiral 4-aza-4-deoxypodophyllo-

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This paper was written on the occasion of the retirement of the first author, Professor Masao Arimoto, from Osaka University of Pharmaceutical Sciences.

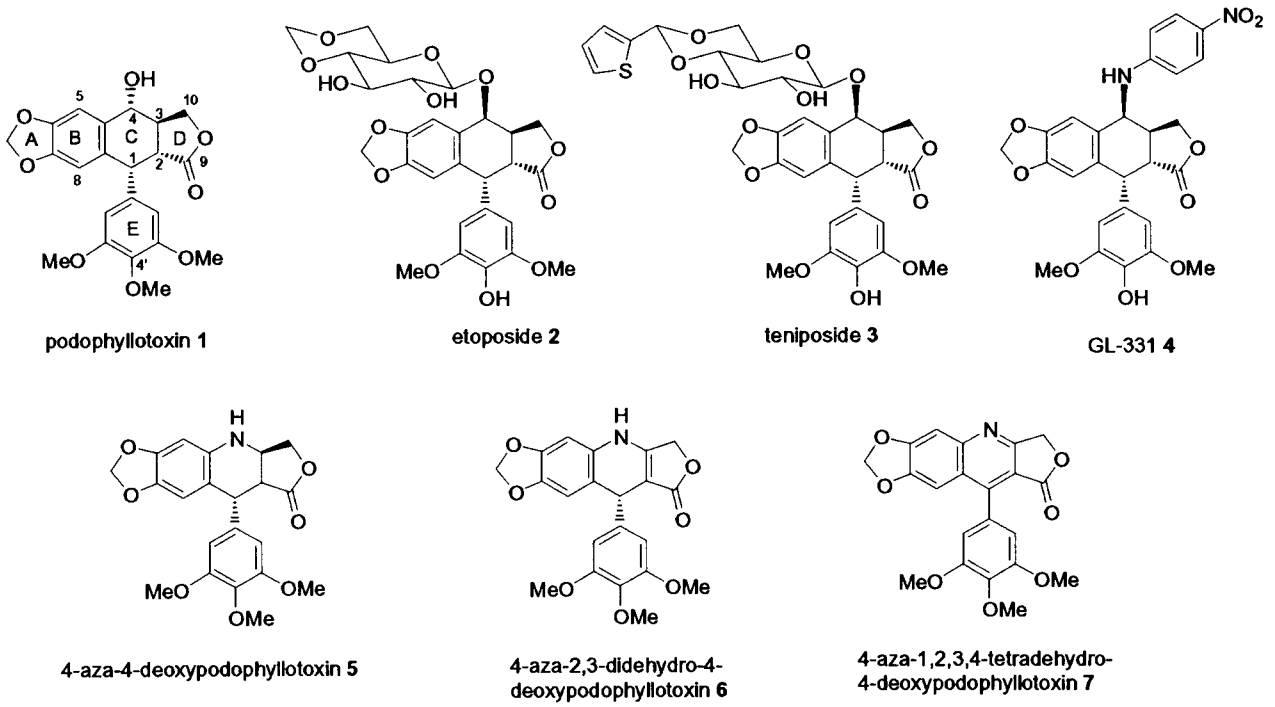


Fig. 1. Structures of podophyllotoxin and analogues

toxin (4-aza-4-deoxyPDX **5**) using natural **1** as the starting material.[30] Other reports of 4-aza-4-deoxyPDX synthesis, including **5**–**7**, are racemate synthesis or synthesis of compounds without a stereogenic center.[31-35] Then, we attempted to perform the chiral synthesis of 4-aza-4-deoxyPDXs **5** or **6** using the classic Meyer method[36] and oxazolines derived from amino acids as chiral auxiliary. Herein we report our synthetic study for chiral 4-azaPDXs and also show that the aromatization significantly stabilized the resultant molecules.

RESULTS AND DISCUSSION

Our synthetic approach to chiral 4-azaPDX followed Meyers' successful asymmetric total synthesis of **1** in 1988[36] using diastereoselective Michael addition to naphthalene derivatives with oxazolines as the chiral auxiliary. The introduction of 4-nitrogen to C-ring seemed very attractive as it might allow many chemical modifications, such as *N*-alkylation or *N*-acylation.

The synthesis of novel chiral quinolines is illustrated in Chart 1. Commercially available 6-nitropiperonal (**8**) was reduced to 6-aminopiperonal (**9**) by adding aqueous ammonia with catalytic ferrious sulfate and *c*-hydrochloric acid with vigorous agitation at 90°C.[37] Amine **9** was reacted with β-ketoesters via Friedländer synthesis[38,39] to afford ethyl quinolinecarboxylates (**10**), and these were hydrolyzed to quinolinecarboxylic acids (**11**). Chiral amino alcohols prepared from amino acids were condensed with prepared **11** under Vorbrüggen conditions[40] to yield desired chiral oxazolines (**12**).

Our early attempt at the Michael addition of phenyllithium to **12a** gave not the desired imine-type product but enamine, as observed in the ^{1}H-NMR spectrum of the crude product. The enamine was so unstable that it aromatized easily into **13** during purification by silica gel column chromatography or exposure to air, as illustrated in Chart 2. The ^{1}H-NMR spectrum of crude enamine had two broad signals around 5.14 ppm corresponding to two H-1 protons of the diastereomers.

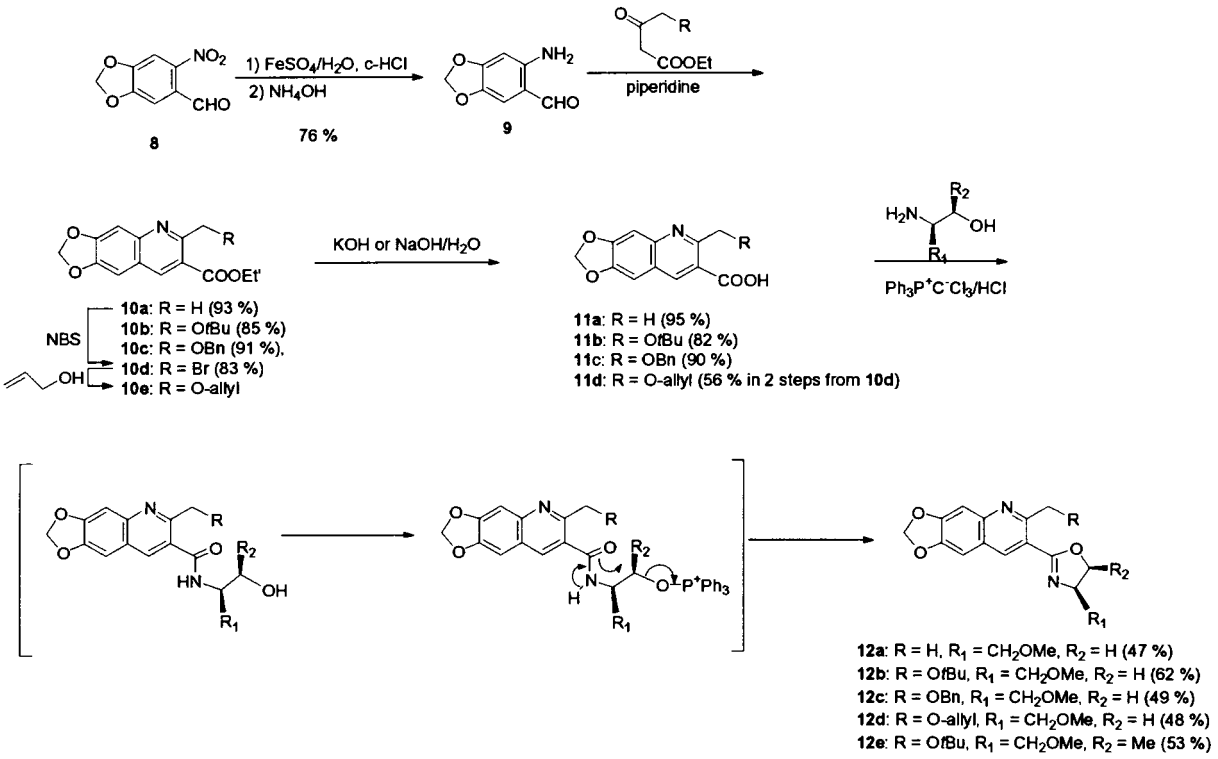


Chart 1. Synthesis of chiral oxazoline-quinolines via Friedländer's method

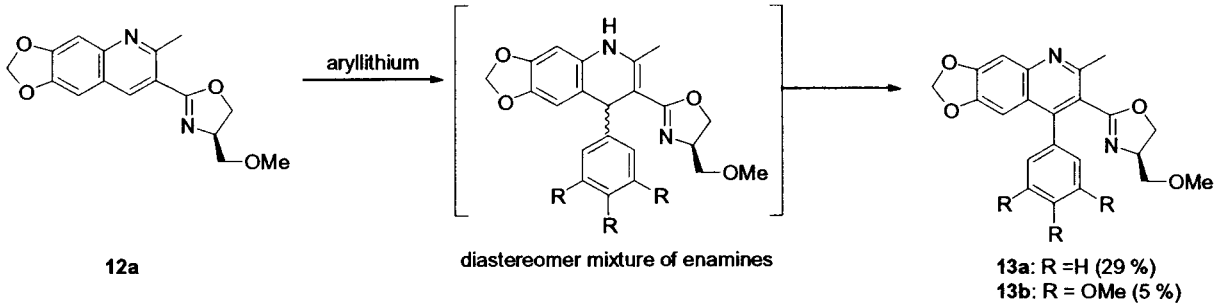
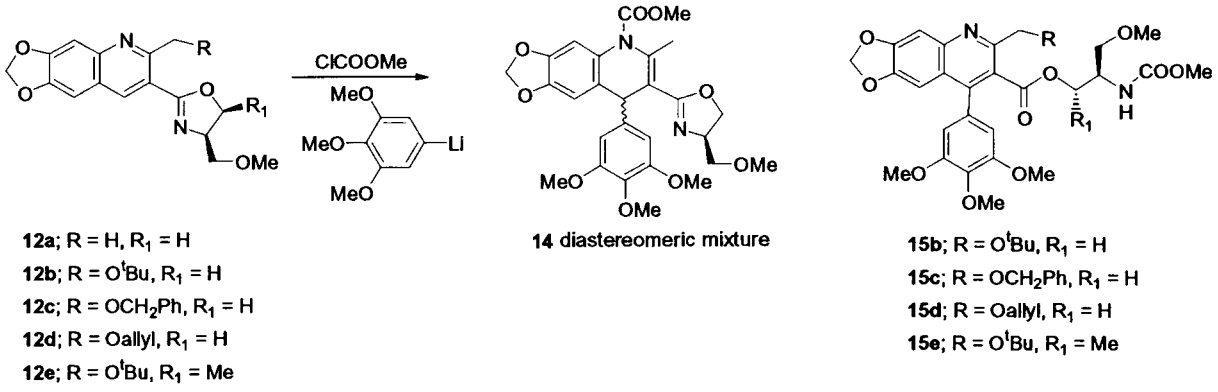


Chart 2. Michael addition without ClCOOMe

Then, we attempted to trap electrons on the nitrogen atom neighboring the piperonyl ring by adding methyl chloroformate in order to inhibit aromatization. The results are summarized in Chart 3 and Table 1. As seen in entry 1, Michael adduct **14**, which was a mixture of inseparable diastereomers in the ratio of 78:22 as shown by NMR analysis and whose relative stereochemistry could not be determined, was obtained only when R = H.

But all other trials gave complex mixtures. Most of materials were lost in purification process. Structures



12a; R = H, R_1 = H
12b; R = O^{t}Bu, R_1 = H
12c; R = OCH_2Ph, R_1 = H
12d; R = Oallyl, R_1 = H
12e; R = O^{t}Bu, R_1 = Me

14 diastereomeric mixture

15b; R = O^{t}Bu, R_1 = H
15c; R = OCH_2Ph, R_1 = H
15d; R = Oallyl, R_1 = H
15e; R = O^{t}Bu, R_1 = Me

Chart 3. Michael addition with ClCOOMe

Table 1. Michael addition of aryllithium with ClCOOMe

entry	substrate	product	yield, %
1	**12a**	**14a,b** (78:22)	71 (combined)
2	**12b**	**15b**	6
3	**12c**	**15c**	1
4	**12d**	**15d**	1
5	**12e**	**15e**	2

of undesired products **15**, which were purely isolated with poor yield, were determined by detailed 2D NMR analysis as summarized in Fig. 2.[35] Their formation was explained by oxazoline ring opening.

A plausible mechanism for the oxazoline ring opening is illustrated in Chart 4. Electron trapping might occur not at the desired nitrogen atom (N-1) but at the nitrogen atom in oxazoline during the Michael addition of aryllithium. The tentatively formed adduct might be easily attacked by a hydroxyl anion because of its instability to afford more stable product **15**.

From the results described above, we altered our initial plan of preparing Michael adducts with C-3 chiral oxazoline on C-3 and protected hydroxymethyl

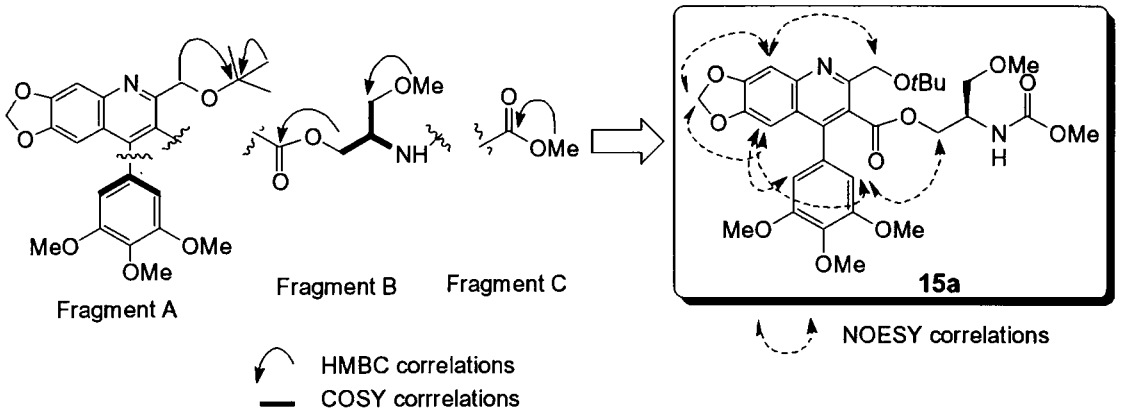


Fig. 2. Structural determination of the reaction product 15a

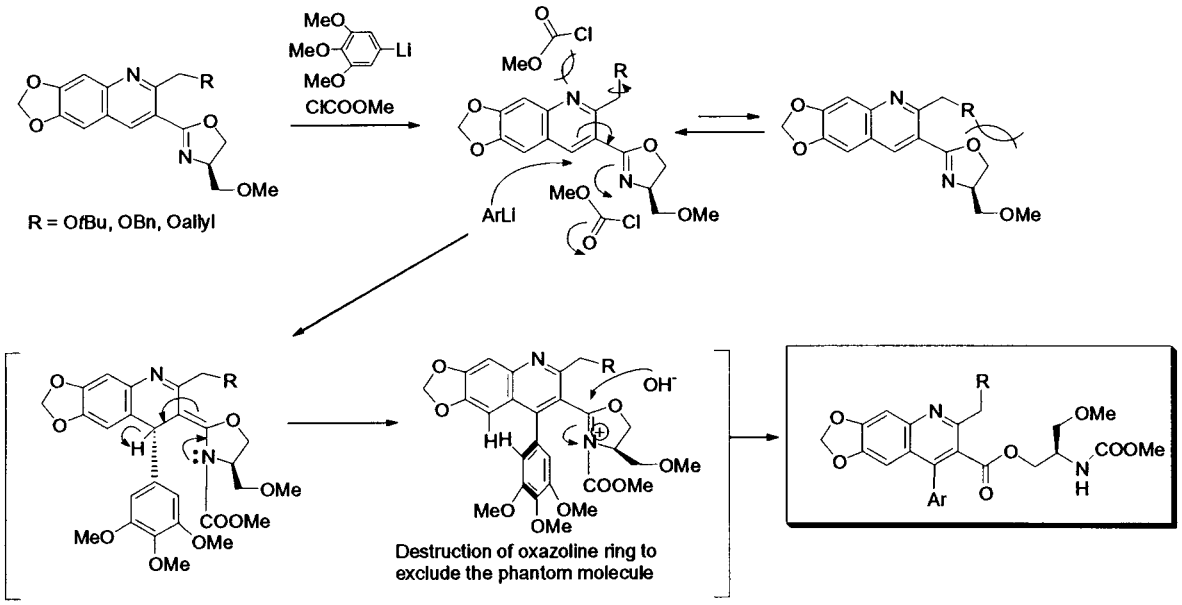


Chart 4. Plausible mechanism for oxazoline ring opening

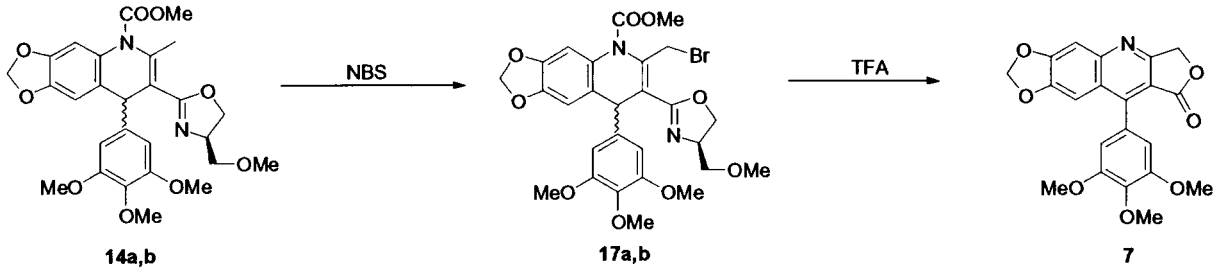


Chart 5. Transformation of 14 to 7

group on C-2 in the quinoline ring. We chose to examine the transformation of successful Michael adduct **14** into 4-aza-4-deoxyPDXs, as summarized in Chart 5. A mixture of Michael adducts **14a**,**b** was treated with NBS in the presence of a catalytic amount of benzoylperoxide to give bromide **17** in 38% yield. Then, **17** was hydrolyzed with TFA followed by cyclization. However, the sequence of reactions resulted in loss of chirality to afford aromatized **7**. We supposed that the aromatization was due to the significant stability of **7**. We reconfirmed that the chirality on the C1-C1' axis in the trimethoxyphenyl group of **7** did not remain based on its specific rotation value of 0.

CONCLUSION

We have synthesized novel quinolines bearing oxazolines as chiral auxiliary and examined the diastereoselective Michael addition of aryllithium to them for the synthesis of the chiral antitumor compound 4-aza-4-deoxypodophyllotoxin (PDX). Most of our attempts at diastereoselective Michael addition resulted in ring opening of oxazoline with aromatization of C-ring in the 4-aza-4-deoxyPDX skeleton, as a result of significant instability of the desired adducts. Only successful Michael adducts with a methyl group at C-2 of quinoline were hydrolyzed and cyclized to afford **7** with loss of the chiral center at C-1. We will continue trying to separate **14a** and **14b**, and will look into other approaches to retain the chirality in 4-azaPDXs once formed.

EXPERIMENTAL

IR spectra were obtained with a JEOL FT/IR-680 Plus spectrometer. HRMS was determined with a JEOL JMS-700 (2) mass spectrometer. NMR spectra were recorded at 27ºC on Varian UNITY INOVA-500 and Mercury-300 spectrometers in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Specific rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Liquid column chromatography was conducted over silica gel (Nacalai, silica gel 60, mesh 70–230 or 230–400). Analytical TLC was performed on precoated Merck glass plates (silica gel 60 F_{254}) and compounds were detected by dipping

the plates in an ethanol solution of phosphomolybdic acid, followed by heating. Dry THF was distilled over sodium benzophenone ketyl under nitrogen atmosphere.

Synthesis of quinolines 10 using Friedländer method

Typical procedure: To a suspension of **9** (6.4 g, 38.8 mmol) with ethyl 3-oxo-butanoate (13.9 mL, 108.8 mmol) in EtOH (100 mL) was added piperidine (13.9 mL, 140.6 mmol) dropwise under nitrogen atmosphere. The reaction mixture was stirred at 40–50ºC for 2 h and refluxed for 30 min. The reaction mixture was acidified with *d*-HCl and the solvent was removed under reduced pressure to afford a residue that was extracted with CH_2Cl_2. The organic layer was successively washed with *d*-HCl, water, and brine, dried over $MgSO_4$, filtered, and evaporated to give a crude mixture that was purified by silica gel column chromatography (eluent: AcOEt:hexane = 1:2) to give quinoline **10a** (9.33 g, 93%).

Ethyl 2-Methyl-6,7-methylenedioxy-3-quinoline-carboxylate 10a: Colorless crystals; mp 155–157ºC; IR (KBr) ν_{max} 1720, 1655, 1620, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.44 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 2.92 (3H, s, Ar-CH_3), 4.42 (2H, q, *J* = 7.2 Hz, -OCH_2CH_3), 6.13 (2H, s, OCH_2O), 7.09 (1H, s, Ar-H), 7.32 (1H, s, Ar-H), 8.55 (1H, s, Ar-H); EIMS *m/z* 259 $(M)^+$; Anal. calcd for $C_{14}H_{13}NO_4$ C, 64.86, H, 5.05, N, 5.40; found C, 64.59, H, 4.99, N, 5.39.

Ethyl 2-*tert*-Butoxymethyl-6,7-methylenedioxy-3-quinolinecarboxylate 10b: Yellow crystals; mp 85–87ºC; IR (Neat) ν_{max} 3474, 1729 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.27 (9H, s, *t*Bu), 1.43 (3H, t, *J* = 7.2 Hz, OCH_2CH_3), 4.42 (2H, q, *J* = 7.2, OCH_2CH_3), 4.95 (2H, s, $ArCH_2O$), 6.13 (2H, s, OCH_2O), 7.08 (1H, s, Ar-H), 7.40 (1H, s, Ar-H), 8.35 (1H, s, Ar-H); HRMS *m/z* calcd for $C_{18}H_{22}NO_5$ $(M)^+$ 331.1420, found 332.1494.

Ethyl 2-Benzyloxymethyl-6,7-methylenedioxy-3-quinolinecarboxylate 10c: Yellow crystals; mp 79–82ºC; IR (KBr) ν_{max} 1720, 1617, 1597 cm^{-1}; ^{1}H-NMR (CDCl3) δ 1.39 (3H, t, *J* = 7.1 Hz, OCH2CH_3), 4.37 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.65 (2H, s, $ArCH_2OBn$), 5.10 (2H, s, OCH_2Ph), 6.13 (2H, s, OCH_2O), 7.09 (1H, s, Ar-H), 7.28–7.39 (5H, s, Ar-H), 7.42 (1H, s, Ar-H), 8.47 (1H, s, Ar-H); EIMS *m/z* 366 (M+H)+; Anal. calcd for $C_21H_{19}NO_5$ C, 69.03, H, 5.24, N, 3.83; found C, 69.14, H, 5.26, N, 3.74.

Ethyl 2-Bromomethyl-6,7-methylenedioxy-3-quinolinecarboxylate 10d: To a solution of **10a** (7.17 g, 27.7 mmol) in CCl_4 (600 mL) were added NBS (7.38 g, 41.5 mmol) and benzoylperoxide (0.14 g, 2.0% w/v) under nitrogen atmosphere, and the reaction mixture was refluxed with stirring for 1 h under of UV light irradiation (200 W). After cooling to rt, CCl_4 was evaporated under reduced pressure to afford a crude residue that was purified by silica gel column chromatography (eluent; 7 % AcOEt in CH_2Cl_2) to give crude bromide, which was further recrystallized from CH_2Cl_2-hexane to yield pure **10d** (7.75 g, 83%). **10d**: Colorless crystals; mp 159–161ºC; IR (KBr) ν_{max} 1720, 1620, 1600, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.47 (3H, t, *J* = 7.0 Hz, OCH_2CH_3), 4.47 (2H, q, *J* = 7.0 Hz, -OCH_2CH_3), 5.15 (2H, s, Ar-CH_2-Br), 6.16 (2H, s, OCH_2O), 7.12 (1H, s, Ar-H), 7.34 (1H, s, Ar-H), 8.62 (1H, s, Ar-H); EIMS *m/z* 337, 339 $(M)^+$; Anal. calcd for $C_{14}H_{12}NO_4Br$ C, 49.73, H, 3.58, N, 4.12; found C, 49.77, H, 3.52, N, 4.23.

Ethyl 2-Allyloxymethyl-6,7-methylenedioxy-3-quinolinecarboxylate 10e: No data because it was used in the subsequent reaction without purification.

Synthesis of 3-quinolinecarboxylic acids 11

Typical procedure: To a solution of **10a** (2.54 g, 9.97 mmol) in 20% MeOH-H_2O (70 mL) was added KOH (1.65 g). After stirring for 2 h at 90–93ºC, methanol was removed under reduced pressure to afford an aqueous solution, and this was adjusted to pH 6-7 with *d*-HCl to

form crystals. The precipitate of product **11a** from the water layer was gathered by suction and recrystallized from EtOH-H_2O to give pure **11a** (2.16 g, 95%)

2-Methyl-6,7-methylenedioxy-3-quinolinecarboxylic Acid 11a: Colorless crystals; mp > 295ºC; IR (KBr) ν_{max} 2800–2400, 1693, 1595 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.79 (3H, s, ArCH_3), 6.22 (2H, s, OCH_2O), 7.30 (1H, s, Ar-H), 7.44 (1H, s, Ar-H), 8.64 (1H, s, Ar-H); ^{13}C-NMR (DMSO-d_6) δ 26.1 (q), 103.4 (t), 104.4 (d), 105.4 (d), 123.2 (s), 123.5 (s), 139.3 (d), 147.8 (s), 148.6 (s), 153.4 (s), 157.0 (s), 168.9 (s); HRMS *m/z* calcd for $C_{12}H_9NO_4$ $(M)^+$ 231.0531, found 231.0533.

2-*tert*-Butoxymethyl-6,7-methylenedioxy-3-quinolinecarboxylic Acid 11b: Colorless crystals; mp 210ºC; IR (Neat) ν_{max} 3463, 1704, 1603 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.16 (9H, s, *t*Bu), 3.38 (1H, br s, OH), 4.77 (2H, s, ArCH_2O), 6.21 (2H, s, OCH_2O), 7.33 (1H, s, Ar-H), 7.41 (1H, s, Ar-H), 8.47 (1H, s, Ar-H); ^{1}H-NMR (MeOH-d_4) δ 1.31 (9H, s, *t*Bu), 5.00 (2H, s, ArCH_2O), 6.19 (2H, s, OCH_2O), 7.30 (1H, s, Ar-H), 7.40 (1H, s, Ar-H), 8.64 (1H, s, Ar-H); ^{13}C-NMR (MeOH-d_4) δ 28.6 (q), 65.8 (t), 74.1 (s), 103.1 (t), 103.9 (d), 105.4 (d), 123.8 (s), 124.8 (s), 137.4 (d), 146.1 (s), 148.4 (s), 152.3 (s), 155.4 (s), 168.4 (s); HRMS *m/z* calcd for $C_{16}H_{18}NO_5$ $(M)^+$ 304.1185, found 304.1170.

2-Benzyloxymethyl-6,7-methylenedioxy-3-quinolinecarboxylic Acid 11c: Colorless crystals; mp 200–210ºC; IR (Neat) ν_{max} 3660–3300, 1700, 1640, 1600 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 4.46 (2H, s, ArCH_2OBn), 5.15 (2H, s, -OCH_2Ph), 6.14 (2H, s, OCH_2O), 7.10 (1H, s, Ar-H), 7.24-7.42 (5H, m, Ar-H), 7.43 (1H, s, Ar-H), 8.57 (1H, s, Ar-H); EIMS *m/z* 338 $(M+H)^+$; Anal. calcd for $C_{19}H_{15}NO_5$ C, 67.65, H, 4.48, N, 4.15; found C, 67.23, H, 4.57, N, 4.08.

2-Allyloxymethyl-6,7-methylenedioxy-3-quinolinecarboxylic Acid 11d

60 % NaH in oil (0.15g, 3.6 mmol) was washed with dry pentane. To the prepared NaH, was added dry THF (10mL). To the resulted suspension was added allylalcohol (0.45 mL, 6.0 mmol) dropwise under nitrogen atmosphere at 0ºC, then **10d** (0.33g, 1.0 mmol) successively. After stirring for 18 hr at rt, 5N NaOH aq (1.4 mL) and water (1.4 mL) were added to the reaction mixture, which was then refluxed for another 2 hr. After cooling, the mixture was diluted with water (5 mL), acidified with 3N HCl aq to almost pH 2, then extracted with CH_2Cl_2. The organic layer was washed with water and brine successively, dried over $MgSO_4$, filtered and evaporated to afford a crude residue, which was purified by silica gel column chromatography (eluent; MeOH : CH_2Cl_2 = 1 : 9) to give **11d** (0.16 g, 56% in 2 steps). **11d**: Yellow crystals; mp 157–160ºC; IR (Neat) ν_{max} 3400–2400, 1700, 1600, 1510 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 4.21 (2H, d, *J* = 6.0 Hz, -OCH_2CH), 5.10 (2H, s, -OCH_2Ph), 5.22 (1H, dd, *J* = 10.5, 1.5 Hz, -CH_2CH=CH*H*), 5.34 (1H, dd, *J* = 15.0, 1.5 Hz, -CH_2CH=C*H*H), 5.99 (1H, ddt, *J* = 15.0, 10.5, 6.0 Hz, -CH_2C*H*=CH_2), 6.16 (2H, s, OCH_2O), 7.14 (1H, s, Ar-H), 7.46 (1H, s, Ar-H), 8.69 (1H, s, Ar-H); EIMS *m/z* 287 $(M)^+$; Anal. calcd for $C_{15}H_{13}NO_5$ C, 62.71, H, 4.56, N, 4.88; found C, 61.80, H, 4.55, N, 4.71.

Synthesis of quinoline-bearing oxazolines 12

Typical procedure: To a solution of quinolinecarboxylic acid **11a** (1.07 g, 4.63 mmol) with (2S)-2-amino-3-methoxypropanol (0.54 g, 5.14 mmol) in pyridine (5 mL)/acetonitrile (5 mL) was added triethylamine (1.94 mL, 13.9 mmol) in CCl_4 (1.43 mL, 14.8 mmol). To the reaction mixture, triphenylphosphine (3.65 g, 13.9 mmol) in pyridine (5 mL)/acetonitrile (5 mL) was added dropwise over 1.5 h under nitrogen atmosphere. After stirring for 33 h at rt, the solvent was removed under reduced pressure below 40ºC to afford a residue that was purified by silica gel column chromatography (eluent: CH_2Cl_2:AcOEt = 5:1 to AcOEt:hexane = 3:1) to

give product **12a** (0.73 g, 47%).

3-{(4*R*)-4-Methoxymethyl-2-oxazolinyl}-2-methyl-6,7-methylenedioxyquinoline 12a: Colorless crystals; mp 99–102ºC; $[\alpha]_D^{22}$ +23.3 (c 0.4, $CHCl_3$); IR (Neat) ν_{max} 1632, 1463 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.91 (3H, s, Ar-CH_3), 3.43 (3H, s, OCH_3), 3.53 (1H, m, -CH*H*OCH$_3$), 3.70 (1H, m, -C*H*HOCH$_3$), 4.32 (1H, dd, *J* = 5.0, 4.6 Hz, -OC*H*HCH-), 4.50 (2H, m, -OCH*H*CH-), 4.56 (1H, m, NC*H*(CH_2)$_2$), 6.11 (2H, s, OCH_2O), 7.01 (1H, s, Ar-H), 7.31 (1H, s, Ar-H), 8.42 (1H, s, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 25.3 (q), 59.3 (q), 66.8 (d), 69.9 (t), 74.6 (t), 101.7 (t), 102.8 (d), 105.0 (d), 119.4 (s), 122.4 (s), 137.0 (d), 146.6 (s), 147.5 (s), 151.8 (s), 155.7 (s), 164.1 (s); HRMS *m/z* calcd for $C_{16}H_{16}N_2O_4$ $(M)^+$ 300.1110, found 300.1109.

2-*tert*-Butoxymethyl-3-{(4R)-4-methoxymethyl-2-oxazolinyl}-6,7-methylenedioxyquinoline 12b: Yellow oil; $[\alpha]_D^{22}$ –8.3 (*c* 2.0, $CHCl_3$); IR (Neat) ν_{max} 1650, 1463, 1231, 1193, 1034 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.27 (9H, s, *t*Bu), 3.43 (3H, s, OCH_3), 3.51 (1H, m, -C*H*HOCH$_3$), 3.71 (1H, m, -C*H*HOCH$_3$), 4.32 (1H, m, -OC*H*HCH-), 4.51 (1H, m, NC*H*), 4.53 (1H, m, -OC*H*HCH-), 4.94 (1H, d, *J* = 10.9 Hz, ArC*H*HO), 5.02 (1H, d, *J* = 10.9 Hz, ArCH*H*O), 6.11 (2H, s, OCH_2O), 7.04 (1H, s, Ar-H), 7.41 (1H, s, Ar-H), 8.39 (1H, s, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 27.8 (q), 59.3 (q), 65.6 (t), 66.6 (d), 70.6 (t), 73.9 (s), 74.7 (t), 101.8 (t), 102.8 (d), 105.9 (d), 119.7 (s), 123.4 (s), 137.5 (d), 146.6 (s), 148.1 (s), 151.8 (s), 155.7 (s), 164.6 (s); HRMS *m/z* calcd for $C_{20}H_{25}N_2O_5$ $(M+H)^+$ 373.1764, found 373.1760.

2-Benzyloxymethyl-3-{(4*R*)-4-methoxymethyl-2-oxazolinyl}-6,7-methylenedioxyquinoline 12c: Yellow oil; $[\alpha]_D^{22}$ +5.0 (*c* 2.2, $CHCl_3$); IR (Neat) ν_{max} 1649, 1462 cm^{-1}; 1H-NMR ($CDCl_3$) δ 3.36 (3H, s, OCH_3), 3.37 (1H, m, -C*H*HOCH$_3$), 3.61 (1H, m, -C*H*HOCH$_3$), 4.26 (1H, m, OCH*H*CH), 4.43 (1H, m, NC*H*), 4.46 (1H, m, OC*H*HCH), 4.65 (2H, s, ArCH_2O), 5.09 (1H, d, *J* = 12.3 Hz, ArCH_2O), 5.14 (1H, d, *J* = 12.3 Hz, ArCH_2O), 6.10 (2H, s, OCH_2O), 7.05 (1H, s, Ar-H), 7.42 (1H, s, Ar-H), 8.43 (1H, s, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 59.2 (q), 66.6 (d), 70.4 (t), 72.6 (t), 72.9 (s), 74.6 (t), 101.9 (t), 102.8 (d), 105.8 (d), 119.3 (s), 123.4 (s), 127.4 (d), 127.9 (d), 128.2 (d), 137.4 (d), 138.3 (s), 146.5 (s), 148.3 (s), 151.9 (s), 154.3 (s), 163.9 (s); HRMS *m/z* calcd for $C_{23}H_{22}N_2O_5$ $(M+H)^+$ 407.1599, found 407.1607.

2-Allyloxymethyl-6,7-methylenedioxy-3-{(4*R*)-4-methoxymethyl-2-oxazolinyl}quinoline 12d: Yellow oil; $[\alpha]_D^{22}$ +20.6 (*c* 0.1, $CHCl_3$); IR (Neat) ν_{max} 1650, 1463, 1235, 1108 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.43 (3H, s, OCH_3), 3.49 (1H, m, -C*H*HOCH$_3$), 3.69 (1H, m, -CH*H*OCH$_3$), 4.31 (1H, m, OC*H*HCH), 4.14 (2H, dt, *J* = 5.7, 1.4 Hz, -OCH_2CH=), 4.44–4.61 (2H, m, NCH and OCH*H*CH), 5.19 (1H, br d, *J* = 10.4 Hz, -CH_2CH=CH*H*), 5.30 (1H, ddd, *J* = 17.2, 1.8, 1.4 Hz, -CH_2CH=C*H*H), 6.00 (1H, ddd, *J* = 17.2, 10.4, 5.7 Hz, -CH_2C*H*=CH_2), 6.13 (2H, s, OCH_2O), 7.06 (1H, s, Ar-H), 7.43 (1H, s, Ar-H), 8.45 (1H, s, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 59.3, 66.6, 70.3, 71.9, 72.5, 74.5, 101.8, 102.7, 105.7, 117.0, 119.0, 123.3, 134.8, 137.3, 146.4, 148.2, 151.8, 154.2, 163.7; HRMS *m/z* calcd for $C_{19}H_{21}N_2O_5$ $(M+H)^+$ 357.1450, found 357.1442.

2-*tert*-Butoxymethyl-3-{(4*R*,5*S*)-4-methoxymethyl-5-methyl-2-oxazolinyl}-6,7-methylenedioxyquinoline 12e: Yellow oil; $[\alpha]_D^{22}$ +46.5 (*c* 1.0, $CHCl_3$); IR (Neat) ν_{max} 1637, 1463 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.27 (9H, s, *t*Bu), 1.47 (3H, d, *J* = 6.6 Hz, CHCH_3), 3.41 (3H, s, OCH_3), 3.60 (1H, dd, *J* = 9.6, 8.0 Hz, -CHC*H*HOCH$_3$), 3.70 (1H, dd, *J* = 9.6, 4.8 Hz, -CHC*H*HOCH$_3$), 4.43 (1H, ddd, *J* = 9.4, 8.0, 4.8 Hz, NC*H*(CH_2)CH), 4.97 (1H, d, *J* = 11.2 Hz, ArC*H*HO-), 4.98 (1H, dq, *J* = 9.4, 6.6 Hz, CH(CH_3)C*H*O-), 5.00 (1H, d, *J* = 11.2 Hz, ArCH*H*O-), 6.10 (2H, s, OCH_2O), 7.04 (1H, s, Ar-H), 7.41 (1H, s, Ar-H), 8.37 (1H, s, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 14.7 (q), 27.8 (q), 59.1 (q), 65.4 (t), 67.8 (d), 71.4 (t), 74.0 (s), 78.4 (d), 101.8 (t), 102.8 (d), 105.9 (d), 120.0 (s), 123.4 (s), 137.3 (d), 146.6 (s), 148.1 (s), 151.7 (s), 155.8 (s),

163.8 (s); HRMS *m/z* calcd for $C_{21}H_{27}N_2O_5$ $(M+H)^+$ 387.1920, found 387.1925.

Michael addition of aryllithium to quinolines (Chart 2, Chart 3, and Table 1)

Typical procedure: A solution of trimethoxyphenyllithium, which was prepared by adding 1.57 M *t*-BuLi in *n*-pentane (10.4 mL, 16.1 mmol) to 3,4,5-trimethoxyphenylbromide (1.99 g, 8.04 mmol) in THF (20 mL) at –78ºC under nitrogen atmosphere, was introduced to a solution of **12a** (0.805 g, 2.68 mmol) in THF (150 mL). After stirring at –78ºC under nitrogen atmosphere for 20 h, methylchloroformate (1.03 mL, 13.4 mmol) was added. Then, the reaction flask was warmed to rt and stirred for another 4 h. After quenching with aq. $NaHCO_3$, the solvent was removed under reduced pressure to afford a residue that was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give a crude mixture that was purified by silica gel column chromatography (eluent: AcOEt:hexane = 3:1) to give a mixture of products **14a** and **14b** (0.996 g, 71%). (*Experiments affording **13a** or **13b** on Chart 2 were carried out without addition of methyl chloroformate.)

3-{(4*R*)-4-Methoxymethyl-2-oxazolinyl}-2-methyl-6,7-methylenedioxy-4-phenylquinoline 13a: Oil; $[\alpha]_D^{22}$ +28.1 (*c* 0.22, $CHCl_3$); IR (Neat) ν_{max} 1662, 1567 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.72 (3H, s, Ar-C*H*$_3$), 3.00 (1H, dd, *J* = 9.4, 7.0 Hz, -C*H*HOCH$_3$), (3H, s, OC*H*$_3$), 3.33 (1H, dd, *J* = 9.4, 4.4 Hz, -C*H*HOCH$_3$), 3.98 (1H, dd, *J* =8.0, 7.0 Hz, -OC*H*HCH-), 4.14 (1H, dd, *J* = 9.4, 8.0 Hz, -OCH*H*CH-), 4.21 (1H, m, CH_2C*H*N=), 6.06 (2H, s, OC*H*$_2$O), 6.79 (1H, s, Ar-H), 7.33 (3H, m, Ar-H), 7.37 (1H, s, Ar-H), 7.45 (2H, dd, *J* = 4.6, 1.8 Hz, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 23.2 (q), 59.1 (q), 66.3 (d), 70.4(t), 74.1 (t), 101.76 (t), 101.85 (d), 105.4 (d), 120.8 (s), 121.9 (s), 128.0 (d), 128.6 (d), 129.2 (d), 129.4 (d),136.2 (s), 146.5 (s), 147.4 (s), 147.7 (s), 151.1 (s), 154.1 (s), 164.0 (s); HRMS *m/z* calcd for $C_{22}H_{20}N_2O_4$ $(M)^+$ 376.1423, found 376.1420.

3-{(4*R*)-4-Methoxymethyl-2-oxazolinyl}-2-methyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl) quinoline 13b: Colorless crystals; mp 120–122ºC; $[\alpha]_D^{22}$ +17.0 (*c* 0.5, $CHCl_3$); IR (Neat) ν_{max} 1663, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.71 (3H, s, Ar-C*H*$_3$), 3.10 (1H, dd, *J* = 9.5, 6.4 Hz, -C*H*HOCH$_3$), 3.32 (3H, s, OC*H*$_3$), 3.60 (1H, dd, *J* =6.4, 4.4 Hz, -C*H*HOCH$_3$), 3.84 (3H, s, Ar-OC*H*$_3$), 3.85 (3H, s, Ar-OC*H*$_3$), 3.94 (3H, s, Ar-OC*H*$_3$), 4.06 (1H, dd, *J* = 7.2, 6.6 Hz, -OC*H*HCH-), 4.20 (1H, t, *J* = 7.2 Hz, -OCH*H*CH-), 4.25 (1H, m, CH_2C*H*N=), 6.08 (2H, s, OC*H*$_2$O), 6.57 (2H, s, Ar-H), 6.91 (1H, s, Ar-H), 7.36 (1H, s, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 23.2, 56.2, 59.2, 61.0, 66.4, 70.4, 74.2, 101.8, 105.4, 106.6, 106.7, 121.9, 127.1, 131.6, 146.5, 147.4, 147.8, 151.2, 152.8, 154.1, 164.1; HRMS *m/z* calcd for $C_{25}H_26N_2O_7$ $(M)^+$ 466.1740, found 466.1736.

***N*-Methoxycarbonyl-3-{(4*R*)-4-methoxymethyl-2-oxazolinyl}-2-methyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-1,4-dihydroquinoline 14a (major), 14b (minor)**: Colorless crystals; mp 60–68ºC; IR (Neat) ν_{max} 1717, 1651, 1589 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 2.478 (3H, s, **14b**-Ar-C*H*$_3$), 2.482 (3H, s, **14a**-Ar-C*H*$_3$), 3.35 (3H, s, **14b**-CH_2OC*H*$_3$), 3.38 (3H, s, **14a**-CH_2OC*H*$_3$), 3.41 (1H, m, -C*H*HOCH$_3$), 3.60 (1H, m, -CH*H*OCH$_3$), 3.72 (3H, s, **14a**-OC*H*$_3$), 3.75 (6H, s, **14b**-OC*H*$_3$), 3.757(3H, s, -OC*H*$_3$), 3.758 (6H, s, -OC*H*$_3$), 4.20 (1H, m, **14a**-OC*H*HCH-), 4.22 (1H, m, **14b**-OC*H*HCH-), 4.38 (1H, m, -CH_2C*H*N=), 4.39 (1H, m, -OCH*H*CH-), 5.13 (1H, s, **14a**-H-1), 5.16 (1H, m, **14b**-H-1), 5.95 (2H, s, **14a**-OC*H*$_2$O), 5.95 (1H, d, *J* = 1.4 Hz , **14b**-OC*H*HO), 5.96 (1H, d, *J* = 1.4 Hz, **14b**-OCH*H*O), 6.427 (2H, s, **14b**-Ar-H), 6.431 (2H, s, **14a**-Ar-H), 6.71 (1H, s, **14b**-Ar-H), 6.74 (1H, s, **14a**-Ar-H), 7.10 (1H, s, **14a**-Ar-H), 7.12 (1H, s, **14b**-Ar-H); ^{13}C-NMR ($CDCl_3$) δ 21.0 (q_{14a}), 21.1 (q_{14b}),

46.2 (d_{14b}), 46.4 (d_{14a}), 53.2 (q_{14a}), 53.2 (q_{14b}), 55.8 (q_{14b}), 55.9 (q_{14a}), 59.2 (q_{14a}), 59.2 (q_{14b}), 60.6 (q_{14a}), 60.6 (q_{14b}), 65.6 (d_{14b}), 65.7 (d_{14a}), 70.3 (t_{14a}), 70.3 (t_{14b}), 74.6 (t_{14a}), 74.7 (t_{14b}), 101.4 (d_{14a}), 101.4 (d_{14b}), 103.7 (d), 103.8 (d_{14b}), 105.8 (d_{14a}), 105.8 (d_{14b}), 106.6 (d_{14a}), 106.6 (d_{14b}), 120.7 (s_{14a}), 120.9 (s_{14b}), 128.2 (s_{14b}), 128.4 (s_{14a}), 131.9 (s_{14a}), 132.1 (s_{14b}), 136.4 (s_{14b}), 136.5 (s_{14a}), 136.7 (s_{14a}), 136.9 (s_{14b}), 153.1 (s_{14b}), 145.1 (s_{14a}), 145.3 (s_{14b}), 145.6 (s_{14a}), 145.6 (s_{14b}), 146.0 (s_{14a}), 146.0 (s_{14b}), 153.1 (s_{14a}), 153.7 (s_{14a}), 153.7 (s_{14b}), 164.7 (s_{14a}), 164.8 (s_{14b});. HRMS *m/z* calcd for $C_{27}H_{30}N_2O_9$ $(M)^+$ 526.1951, found 526.1949.

(2*R*)-2-Amino-*N*-methoxycarbonyl-3-methoxypropyl 2-*tert*-butoxymethyl-6,7-methylenedioxy-3-quinolinecarboxylate 15b: Yellow crystals; mp 174ºC; $[\alpha]_D^{22}$ –2.0 (*c* 2.3, $CHCl_3$); IR (Neat) ν_{max} 3414, 1725, 1616, 1585 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.24 (9H, s, *t*Bu), 3.12 (2H, s, -CHCH_2OCH_3), 3.26 (3H, s, -CH_2OCH_3), 3.64 (3H, s, Ar-OCH_3), 3.78 (1H, m, -CH_2C*H*NH), 3.84 (3H, s, Ar-OCH_3), 3.86 (3H, s, Ar-OCH_3), 3.93 (3H, s, Ar-OCH_3), 4.16 (2H, d, *J* = 4.3 Hz, -OCH_2CH), 4.82 (1H, d, *J* = 13.0 Hz, ArCH*H*O-), 4.84 (2H, d, *J* = 13.0 Hz, ArC*H*HO-), 5.05 (1H, brd, *J* = 8.0 Hz, N*H*), 6.10 (2H, s, OCH_2O), 6.53 (1H, d, *J* = 1.8 Hz, Ar-H), 6.56 (1H, d, *J* = 1.8 Hz, Ar-H), 6.92 (1H, s, Ar-H), 7.39 (1H, s, Ar-H); ^{13}C-NMR ($CDCl_3$) δ 27.4 (q), 49.3 (d), 52.0 (q), 56.1 (q), 56.2 (q), 58.8 (q), 60.9 (q), 63.8 (t), 66.0 (t), 70.6 (t), 74.8 (s), 101.7 (d), 101.9 (t), 105.7 (d), 106.2 (d), 106.4 (d), 123.0 (s), 124.5 (s), 131.5 (s), 138.0 (s), 145.6 (s), 145.6 (s), 148.4 (s), 151.3 (s), 153.23 (s), 153.26 (s), 154.2 (s), 156.4 (s), 168.2 (s); HRMS *m/z* calcd for $C_{31}H_{38}N_2O_{11}$ $(M)^+$ 614.2476, found 614.2479.

(2*R*)-2-Amino-*N*-methoxycarbonyl-3-methoxypropyl 2-benzyloxymethyl-6,7-methylenedioxy-3-quinolinecarboxylate 15c: Yellow oil; $[\alpha]_D^{22}$ –3.0 (*c* 0.11, $CHCl_3$); IR (Neat) ν_{max} 3404, 1725, 1584 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.05 (2H, m -CHCH_2OCH_3), 3.21 (3H, s, -CH_2OCH_3), 3.62 (3H, s, OCH_3), 3.75 (1H, m, -CH_2C*H*NH), 3.845 (3H, s, OCH_3), 3.853 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.00 (2H, m, -OCH_2CH), 4.57 (2H, s, -OCH_2Ar), 4.90 (2H, s, -OCH_2Ar), 4.90 (1H, overlapped, N*H*), 6.11 (2H, s, OCH_2O), 6.55 (1H, d, *J* = 1.8 Hz, Ar-H), 6.56 (1H, d, *J* = 1.8 Hz, Ar-H), 6.93 (1H, s, Ar-H), 7.20–7.39 (5H, m, Ph), 7.41 (1H, s, Ar-H); HRMS *m/z* calcd for $C_{34}H_{36}N_2O_{11}$ $(M)^+$ 643.2319, found 648.2314.

(2*R*)-2-Amino-*N*-methoxycarbonyl-3-methoxypropyl 2-allyloxymethyl-6,7-methylenedioxy-3-quinolinecarboxylate 15d: Oil; $[\alpha]_D^{22}$ –6.0 (*c* 0.1, $CHCl_3$); IR (Neat) ν_{max} 3333, 1731, 1584 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.14 (2H, d, *J* = 5.5 Hz, -CHCH_2OCH_3), 3.27 (3H, s, -CH_2OCH_3), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.05 (2H, d, *J* = 5.7 Hz, -OCH_2CH=CH_2), 4.13 (3H, m, -OCH_2CHNH-, -CH_2C*H*NH-), 4.85 (2H, s, *J* = 12.6 Hz, ArCH_2O-), 4.96 (1H, brd , *J* = 9.0 Hz, N*H*), 5.20 (1H, br d, *J* = 10.5 Hz, -CH_2CH=CH*H*), 5.28 (1H, br d, *J* = 17.2 Hz, -CH_2CH=C*H*H), 5.91 (1H, m, -CH_2C*H*=CH_2), 6. 11 (2H, s, OCH_2O), 6.55 (1H, br s, Ar-H), 6.56 (1H, br s, Ar-H), 6.93 (1H, s, Ar-H), 7.41 (1H, s, Ar-H); HRMS *m/z* calcd HRMS *m/z* calcd for $C_{30}H_{34}N_2O_{11}$ $(M)^+$ 598.2163, found 598.2169.

(1*S*,2*R*)-2-Amino-1-methyl-*N*-methoxycarbonyl-3-methoxypropyl 2-*tert*-butoxymethyl-6,7-methylenedioxy-3-quinolinecarboxylate 15e: Oil; $[\alpha]_D^{22}$ +48.0 (*c* 0.3, $CHCl_3$); IR (Neat) ν_{max} 3333, 1724, 1615, 1584 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.04 (3H, d, *J* = 6.2 Hz, -CHCH_3), 1.26 (9H, s, *t*Bu), 3.27 (3H, s, -CH_2OCH_3), 3.27 (1H, m, -CHC*H*HOCH_3), 3.29 (1H, m, -CHCH*H*OCH_3), 3.64 (3H, s, OCH_3), 3.825 (3H, s, OCH_3), 3.83 (1H, m, -CH_2C*H*NH-), 3.832 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.82 (1H, d, *J* = 12.6 Hz, ArCH*H*O-), 4.87 (2H, d, *J* = 12.6 Hz, ArC*H*HO-), 5.06 (1H, qd, *J* = 6.2, 3.8 Hz, -COOC*H*CH(CH_3)-), 5.72 (1H, br-d, *J* = 8.7 Hz, N*H*), 6.08 (2H, s, OCH_2O), 6.47 (1H, d, *J* = 1.8 Hz, Ar-H), 6.52 (1H, d, *J* = 1.8 Hz, Ar-H), 6.84

(1H, s, Ar-H), 7.37 (1H, s, Ar-H); HRMS *m/z* calcd for $C_{32}H_{40}N_2O_{11}$ $(M)^+$ 628.2632, found 628.2633.

***N*-Methoxycarbonyl-3-{(4*R*)-4-methoxymethyl-2-oxazolinyl}-2-bromomethyl-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-1,4-dihydroquinoline 17**

To a solution of **14a** and **14b** (68.6 mg, 0.13 mmol) in CCl_4 (5 mL) were added NBS (23.3 mg, 0.13 mmol) and benzoylperoxide (1.2 mg, 0.04 mmol) under nitrogen atmosphere, and the reaction mixture was refluxed with stirring for 24 h. After extracting with CH_2Cl_2, the organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude residue that was purified by silica gel column chromatography (eluent: hexane:AcOEt = 1:2 to CH_2Cl_2:AcOEt = 4:1) to give bromide **17a** and **17b** (30 mg, 38%). **17a** and **17b** (mixture of diastereomers): Pale yellow crystals; mp 60–68ºC; IR (Neat) ν_{max} 1718, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.37 (3H, s, **17b**-OC*H*$_3$), 3.38 (3H, s, **17a**-OC*H*$_3$), 3.43 (1H, dd, *J* = 9.7, 5.7 Hz, -C*H*HOCH$_3$), 3.63 (1H, dd, *J* = 9.7, 3.7 Hz, CH*H*OCH$_3$), 3.72 (3H, s, **17a**-Ar-OC*H*$_3$), 3.745 (3H, s, **17b**-Ar-OC*H*$_3$),3.75 (6H, s, Ar-OC*H*$_3$), 3.76 (3H, s, Ar-OC*H*$_3$), 4.27 (1H, m, -OC*H*HCH-), 4.43 (1H, m, -CH$_2$C*H*N=), 4.45 (1H, m, -OCH*H*CH-), 4.86 (1H, d, *J* = 10.8 Hz, **17b**-ArC*H*HBr), 4.89 (1H, d, *J* = 11.0 Hz, **17a**-ArC*H*HBr), 5.17 (1H, s, **17a**-H-1), 5.23 (1H, s, **17b**-H-1), 5.43 (1H, d, *J* = 10.8 Hz, **17b**-ArCH*H*Br), 5.44 (1H, d, *J* = 11.0 Hz, **17a**-ArCH*H*Br), 5.99 (2H, s, **17a**-OC*H*$_2$O), 6.00 (2H, s, **17b**-OC*H*$_2$O), 6.39 (2H, s, **17a**-Ar-H), 6.40 (2H, s, **17b**-Ar-H), 6.70 (1H, s, **17b**-Ar-H), 6.73 (1H, s, **17a**-Ar-H), 7.11 (1H, s, **17a**-Ar-H). 7.13 (1H, s, **17b**-Ar-H); HRMS *m/z* calcd for $C_{27}H_{29}N_2O_9{}^{79}Br$ $(M)^+$ 604.1056, found 604.1055; calcd for $C_{27}H_{29}N_2O_9{}^{81}Br$ $(M)^+$ 606.1036, found 606.1035.

4-Aza-1,2,3,4-tetradehydro-4-deoxypodophyllotoxin 7

To a solution of bromide **17a**,**b** (66.7 mg, 0.11 mmol) in THF (2 mL) was added trifluoroacetic acid (41 μL, 0.55 mmol) under nitrogen atmosphere, and the reaction mixture was heated at 90ºC with stirring overnight. After removing trifluoroacetic acid under reduced pressure, water (0.1 mL) and K_2CO_3 (20 mg) were added and the mixture was heated at 90ºC with stirring for another 4 h. After extracting with CH_2Cl_2, the organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford a crude residue that was purified by silica gel column chromatography (eluent: CH_2Cl_2:AcOEt = 3:1) to give aromatized product **7** (18.0 mg, 36%). **7**: Colorless crystals; mp 243–245ºC; $[\alpha]_D{}^{22}$ 0 (*c* 0.9, $CHCl_3$); IR (Neat) ν_{max} 1777, 1506, 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.86 (6H, s, Ar-OC*H*$_3$), 3.97 (3H, s, Ar-OC*H*$_3$), 5.37 (2H, s, Ar-C*H*$_2$O), 6.18 (2H, s, OC*H*$_2$O), 6.60 (2H, s, Ar-H), 7.19 (1H, s, Ar-H), 7.45 (1H, s, Ar-H); HRMS *m/z* calcd for $C_{23}H_{23}NO_8(M)^+$ 395.1005, found 395.1007.

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