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SELECTIVE *N*-DEMETHYLATION OF TERTIARY AMINOFUMAGILLOLS WITH SELENIUM DIOXIDE *VIA* A NON-CLASSICAL POLONOVSKI TYPE REACTION

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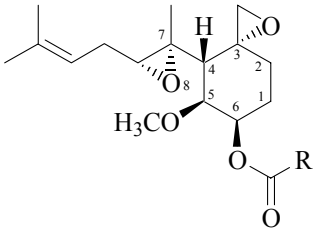
Abstract - The previously unknown selective *N*-demethylation of tertiary aminofumagillols (**5a-e**) to the corresponding secondary aminofumagillols (**7a-e**) is effectively accomplished *via* a non-classical Polonovski type reaction using selenium dioxide (SeO_2). Especially, noteworthy is that two epoxy and the α,β-unsaturated ester functionalities in the fumagillol molecules tolerate in this transformation. Aminofumagillol derivatives are valuable antiangiogenesis inhibitors.

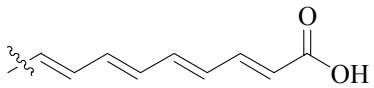
Fumagillin (**1a**), a natural product isolated from *Aspergillius fumigatus*, irreversibly binds to methionine aminopeptidase 2 (MetAP2) and has been shown to inhibit the growth of endothelial cell proliferation.[1] Folkman *et al.* proposed that the inhibition of angiogenesis is potentially a promising approach for the

cancer treatment.[2] A variety of fumagillol analogues including TNP-470 (**1b**)[3] and CKD-732 (**1c**)[4] have been previously prepared (**Scheme 1**). In the course of the studies of metabolites of CKD-732, we found a compound proposed as *N*-mono-demethylated CKD-732 (**7a**) by HPLC/MS analysis which was one of the significant and active metabolite in human plasma. In order to confirm and identify the exact structure and biological activity, we tried to synthesize this proposed compound. The selective *N*-dealkylation of tertiary amines is an important reaction in organic synthesis. Especially, our CKD-732 (**1c**), having two epoxides (spiro-epoxide and the one on C4 alkene side chain) and the α,β-unsaturated ester moiety at C6 the dealkylation, needed strict choice of reagents.



1

1a Fumagillin R =



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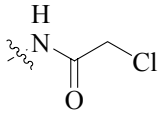
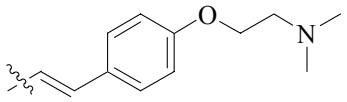


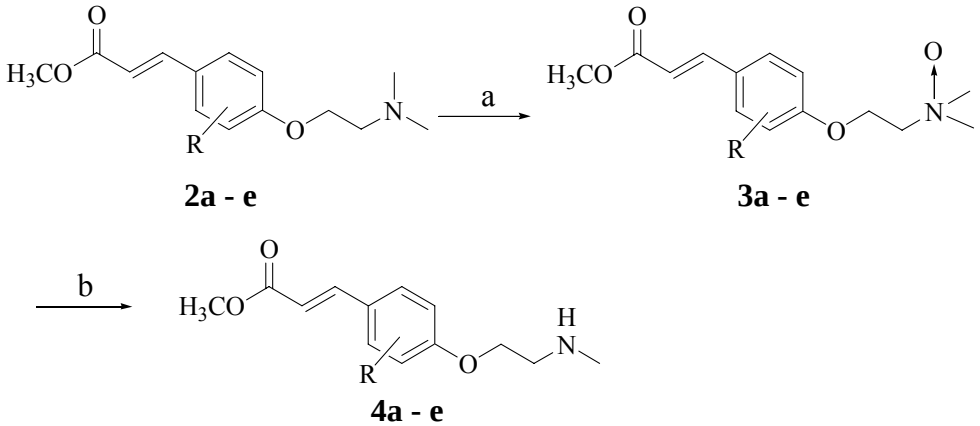
1c CKD-732 R =



Scheme 1

There are a number of general methods for the dealkylation of tertiary amines described in the literature. The classical von Braun reaction using cyanogen bromide[5] is frequently used. The use of alkyl chlorocarbonate[6,7] has been found to complement cyanogen bromide. Several other reagents such as azidocarboxylic esters, nitrous acid, and potassium chromate have also been used.[8] Moreover, de-*N*-alkylation via amine *N*-oxide known as Polonovski reaction[9] has been developed. In the conventional Polonovski reaction, tertiary amine *N*-oxides are generally treated with acetic anhydride (Ac_2O) or

trifluoroacetic anhydride (TFAA) for the dealkylation to provide iminium ions which are converted into enamines and aldehydes under the isolation conditions employed.[9] Recently, the non-classical Polonovski reaction using iron salts[10-12] has also been reported. However, our attempts converting our tertiary amines into the corresponding secondary amines have been unsuccessful under these conventional conditions because of ring-opening of the spiroepoxide moiety at the C3 position to generate some extent of the C6-aldehyde. With the aim to attain selective *N*-demethylation of tertiary aminofumagillols to the corresponding *N*-demethylated aminofumagillols without any another side products, our extensive efforts were focused on the selenium dioxide (SeO_2) which was reported by Sharpless and Lauer[13] in 1972. We now wish to disclose that this selective *N*-demethylation transformation can be effectively and conveniently accomplished *via* a non-classical Polonovski type reaction using selenium dioxide. In addition, another advantage of this procedure is capability of carrying out simply and mildly under virtually neutral reaction conditions. First, in order to find optimal conditions, we tried model studies with suitable tertiary amine *N*-oxides (**3a-e**) having an α,β-unsaturated ester functionality in their molecules (Scheme 2).



R : *meta* - H, Br, OCH_3

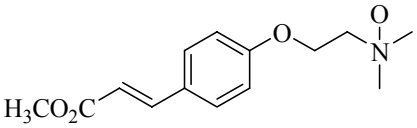
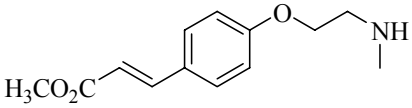
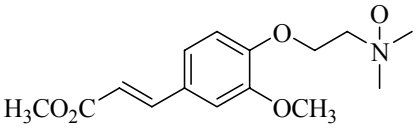
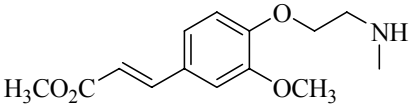
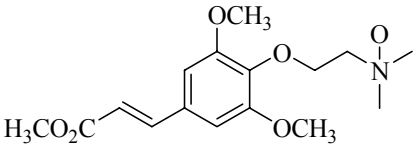
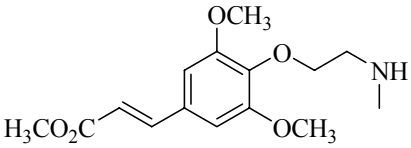
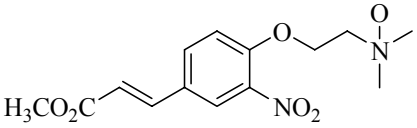
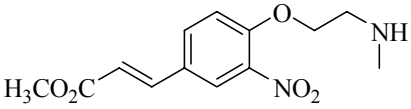
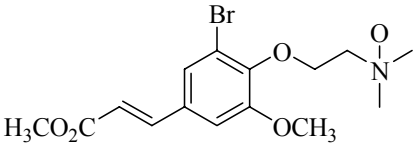
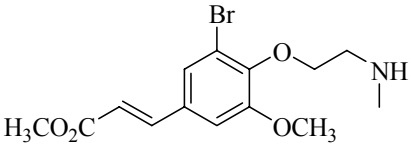
Reagents and conditions : a) 30% H_2O_2, acetone, rt, 5-7 h, 65-85%; b) SeO_2, EtOH, reflux, 3-5 h, 65-83%

Scheme 2

The procedure is very simple. The tertiary aminoethoxycinnamic acid methyl esters (**2a-e**) were first converted into the corresponding *N*-oxides (**3a-e**) in 65-85% yields by oxidation with 30% hydrogen

peroxide in acetone at room temperature for 5-7 h, respectively. Subsequent treatment of the *N*-oxides (**3a-e**) with selenium dioxide in ethanol at reflux for 3-5 h provided the corresponding *N*-demethylated secondary amines (**4a-e**) selectively in 65-83% yields without any significant by-products, respectively.

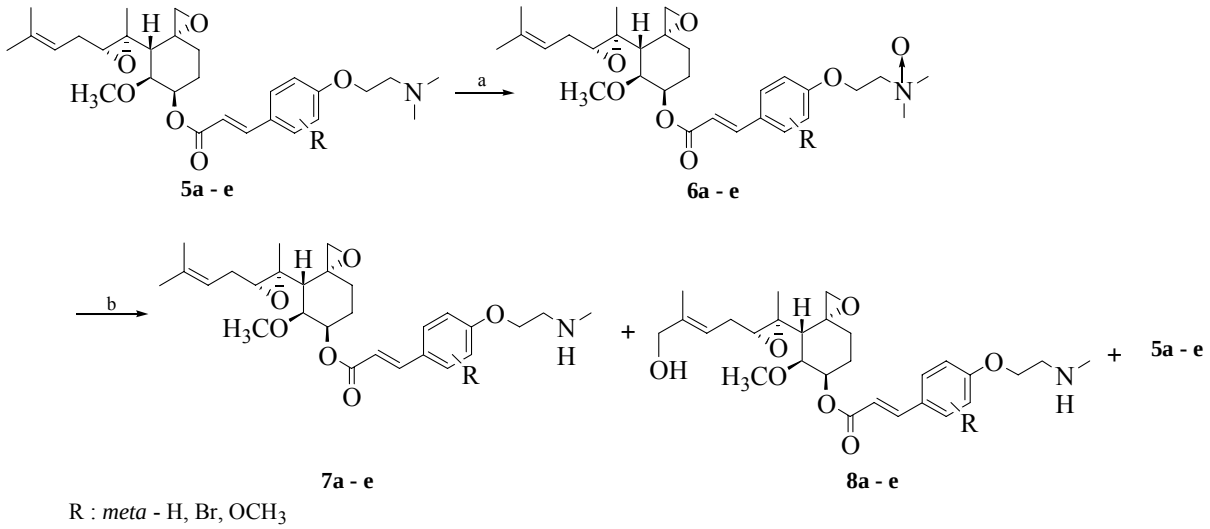
Table 1. Selective *N*-demethylation of the *N*-oxides (3) with SeO_2 in ethanol[a,b)]

Substrate	Product	Conditions: Time (h)	Yield[c)] (%)
 **3a**	 **4a**	**5**	**78**
 **3b**	 **4b**	**3**	**80**
 **3c**	 **4c**	**3**	**83**
 **3d**	 **4d**	**4**	**65**
 **3e**	 **4e**	**3**	**70**

a) All reactions were monitored by HPLC or TLC. b) To a solution of substrates (**3a-e**) (1.0 mmol) in 95% EtOH was added SeO_2 (1.5 mmol, 1.5 equiv) at rt. The reaction mixture was then stirred at reflux temperature.
c) Isolated yields

As shown in Table 1, 4-*N*,*N*-dimethylaminoethoxycinnamic acid methyl ester *N*-oxide (**3a**) and its analogs (**3b-c**) were converted to the corresponding secondary amines (**4a-c**) in 78-83% to moderate

yields by selective *N*-demethylation with selenium dioxide at reflux in ethanol. However, in the cases of the *N*-oxides (**3d-e**) having functionality on the aromatic ring, they gave the corresponding secondary aminoethoxycinnamic acid methyl esters (**4d-e**) in slightly decreased yields (65-70%), but exhibited good *N*-demethylation selectivity without any significant by-products. The results are summarized in Table 1.



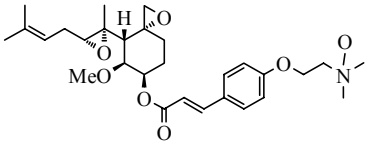
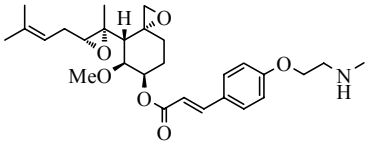
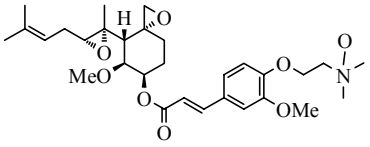
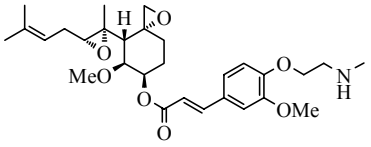
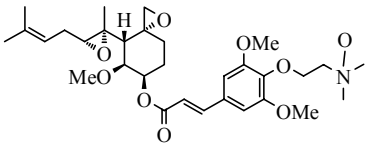
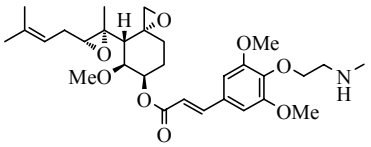
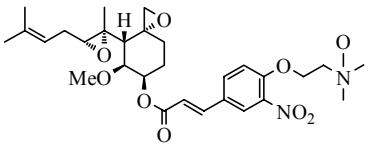
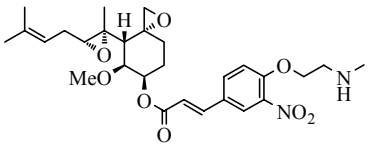
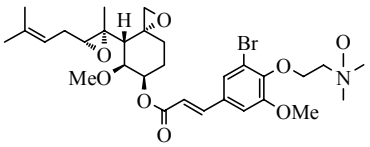
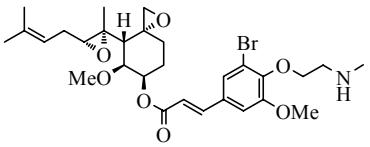
Reagents and conditions : a) 30% H_2O_2, acetone, rt, 5-8 h, 60-80%; b) SeO_2, EtOH, reflux, 2.5-5 h, 62-85%

Scheme 3

Based on this model study, we tried to apply for selective *N*-demethylation of our novel tertiary aminoethoxyfumagillol compounds. The previously unknown selective *N*-demethylation of tertiary aminofumagillol *N*-oxides (**6a-e**) was effectively accomplished *via* a non-classical Polonovski type reaction using selenium dioxide (SeO_2) to give the corresponding secondary aminoethoxyfumagillols (**7a-e**). Especially, two epoxy and the α,β-unsaturated ester functionalities in the fumagillol framework tolerated in this transformation as depicted in Scheme 3. The same procedure was applied successfully to other tertiary aminofumagillol compounds to give the coresponding secondary amines. First, tertiary aminofumagillols (**5a-e**) were transformed into the corresponding *N*-oxides (**6a-e**) in 60-80% yield by oxidation with 30% hydrogen peroxide in acetone at room temperature for 5-8 h. Subsequent treatment of the *N*-oxides (**6a-e**) with selenium dioxide (SeO_2) in ethanol at reflux condition for 2.5-5 h provided the

corresponding secondary aminofumagillol derivatives (**7a-e**) *via* a non-classical Polonovski type reaction in 62-85% yields without formation of any significant by-products, respectively (Scheme 3). In the cases of *N*,*N*-dimethylaminofumagillol *N*-oxide (**6a**) and their mono and dimethoxy- derivative (**6b** and **6c**), these compounds were effectively and selectively transformed into the corresponding secondary aminoethoxyfumagillol derivatives (**7a-c**) in good yields (77-85%) (Table 2). However, the *N*-oxides (**6d-e**) having electron withdrawing group on the aromatic ring gave the corresponding secondary aminoethoxyfumagillols (**7d-e**) in slightly decreased yields (62-65%), exhibiting a moderate selective *N*-demethyaltion without any significant by-products. The results are summarized in Table 2. In order to confirm and identify, the synthetic mono-*N*-methylated aminoethoxyfumagillol (**7a**) was compared with the observed compound in human plasma (HPLC / MS system *m/z* 486 $(M+H)^+$, HPLC retention time 14.2 min). As a result, the synthetic secondary amine (**7a**) was identical with the active metabolite derived from CKD-732 (**1c**). It is interesting that de-ethoxylated aminofumagillols and de-benzylated aminofumagillols were not observed, whereas the classical Polonovski reaction of *p*-substituted *N*-benzylamino compounds afforded the corresponding debenzylated product (major) and the demethylated product (minor).[14] The selective demethylation of the aminofumagillol *N*-oxides in the presence of selenium dioxide could be explained by the marked preference for oxidation at the methyl center of *N*-methyl substituted amine oxide.[11] In summary, we have demonstrated for the first time that reaction of the aminofumagillol *N*-oxides (**6a-e**), possessing two epoxides and the α,β-unsaturated ester moiety, affords the corresponding secondary aminofumagillol derivatives (**7a-e**) selectively in moderated yields (62-85%) *via* a non-classical Polonovski type reaction. However, unexpectedly, all of substrates gave a small amount of by-products, which were proved as allylic oxidation compounds (**8a-e**) and *N*-deoxygenated tertiary aminofumagillols (**5a-e**). The allylic oxidation compounds were not the major by-products but the minor products generating in 4-15% yields. The *N*-deoxygenated tertiary aminofumagillols (**5a-e**) were detected as the major by-products (about 8-20% yields).

Table 2. Selective *N*-demethylation of fumagillol derivatives with SeO_2 in ethanol[a,b)]

Substrate	Product	Conditions Time (h)	Yield[c)] (%)
 **6a**	 **7a**	**3**	**77**
 **6b**	 **7b**	**2.5**	**82**
 **6c**	 **7c**	**2.5**	**85**
 **6d**	 **7d**	**4**	**62**
 **6e**	 **7e**	**5**	**65**

a) All reaction were monitored by HPLC or TLC. b)To a solution of substrates (**6a**-**e**) (1.0 mmol, 1.0 equiv.) in 95% EtOH was added SeO_2 (1.5 mmol, 1.5 equiv.) at rt. The reaction mixture was then stirred at reflux temperature.
c) Isolated yields.

EXPERIMENTAL

Commercially available reagents were used without purification. All reactions were conducted under anhydrous conditions in solvents dried over molecular sieves type 4Å under nitrogen atmosphere and performed using oven dried glassware. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrophotometer. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400 MHz for proton and 100 MHz for carbon NMR and were performed in DMSO-d_6 and $CDCl_3$ solution using tetramethylsilane as the internal reference and chemical shift (δ) is reported in ppm downfield from internal tetramethylsilane. The coupling constants (*J*) are reported in Hz. MS spectra were recorded on a HP 5989B instrument. The HPLC/MS system consists of an HP1100 liquid chromatograph (Agilent; Palo Alto, CA, USA) and a LC/MSD ion trap mass spectrometer equipped with an ESI source (Agilent). An RP-18 GP column (4.6 x 250 mm, particle size 5 m) for the HPLC analysis was purchased from Kanto Chemical Co (Tokyo, Japan). Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) according to the published procedure.[15] TLC was performed on glass backed plates pre-coated with silica (0.2 mm, 60 F_{254}) and developed using standard visualizing agents UV fluorescence (254 and 365 nm), potassium permanganate and iodine.

General procedures: preparation of 3-[4-(2-Dimethylaminoethoxy)phenyl]acrylic acid methyl ester *N*-oxide (3a). To a mixture of 3-[4-(2-dimethylaminoethoxy)phenyl]acrylic acid methyl ester (**2a**) (2.49 g, 10 mmol) in 50 mL of acetone was added dropwise 37.7 mL (4.0 mmol) of 30% hydrogen peroxide solution for 30 min at 0-5 °C, and the resulting mixture was stirred at room temperature for 5-8 h. The reaction mixture was concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatography through a silica gel column, using a gradient elution method, with a mixture of dichloromethane and methanol, in ratios ranging from 20:1 to 10:1 by volume, as the eluent, to give 2.25g of 3-[4-(2-dimethylaminoethoxy)phenyl]acrylic acid methyl ester *N*-oxide (**3a**) as a pale yellow solid: yield 85%; mp 125-127 °C ; ^{1}H-NMR ($CDCl_3$) δ: 7.63 (1H, d, *J* = 16.0 Hz), 7.48 (2H, d,

J = 8.7 Hz), 6.92 (2H, d, *J* = 8.7 Hz), 6.32 (1H, d, *J* = 16.0 Hz), 4.63 (2H, t, *J* = 4.2 Hz), 3.79 (3H, s), 3.77 (2H, t, *J* = 4.2 Hz), 3.36 (6H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.0, 159.3, 145.2, 131.5, 127.3, 119.4, 115.1, 114.6, 72.4, 60.5, 50.5, 42.3; IR (KBr) cm^{-1}: 3424, 1700, 1604, 1251, 1185; HR-MS (ESI) Calcd for $C_{14}H_{20}NO_4$ $(M+H)^+$: 266.1392. Found: 266.1397; *Anal*. Calcd for C, 63.38; H, 7.22; N, 5.28. Found C, 63.67; H, 7.28; N, 5.24.

3-[4-(2-Dimethylaminoethoxy)-3-methoxyphenyl]acrylic acid methyl ester *N*-oxide (3b). This compound was prepared using the same procedure as for the preparation of **3a**: yield 78%; mp 127-129 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.64 (1H, d, *J* = 16.0 Hz), 7.49 (1H, d, *J* = 8.7 Hz), 7.45 (1H, s), 6.96 (1H, d, *J* = 8.7 Hz), 6.29 (1H, d, *J* = 16.0 Hz), 4.56 (2H, t, *J* = 4.2 Hz), 3.81 (3H, s), 3.76 (2H, t, *J* = 4.2 Hz), 3.72 (3H, s), 3.38 (6H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.1, 153.6, 145.7, 141.3, 130.3, 120.1, 119.7, 115.3, 113.6, 72.1, 59.8, 57.1, 50.5, 41.6; IR (KBr) cm^{-1}: 3422, 1702, 1601, 1252, 1186; HR-MS (ESI) Calcd for $C_{15}H_{22}NO_5$ $(M+H)^+$: 296.1498. Found: 296.1493; *Anal*. Calcd for C, 61.00; H, 7.17; N, 4.74. Found C, 59.54; H, 7.54; N, 4.81.

3-[4-(2-Dimethylaminoethoxy)-3,5-dimethoxyphenyl]acrylic acid methyl ester *N*-oxide (3c). This compound was prepared using the same procedure as for the preparation of **3a**: yield 73%; mp 131-132 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.63 (1H, d, *J* = 16.0 Hz), 7.52 (2H, s), 6.31 (1H, d, *J* = 16.0 Hz), 4.51 (2H, t, *J* = 4.2 Hz), 3.80 (3H, s), 3.72 (2H, t, *J* = 4.2 Hz), 3.74 (6H, s), 3.37 (6H, s); ^{13}C-NMR ($CDCl_3$) δ: 169.2, 155.5, 147.1, 132.7, 120.6, 115.5, 114.0, 72.7, 59.4, 57.7, 51.2, 41.5; IR (KBr) cm^{-1}: 3423, 1701, 1601, 1251, 1191; HR-MS (ESI) Calcd for $C_{16}H_{24}NO_6$ $(M+H)^+$: 326.1604. Found: 326.1601; *Anal*. Calcd for C, 59.06; H, 7.13; N, 4.31. Found C, 59.44; H, 7.23; N, 4.45.

3-[4-(2-Dimethylaminoethoxy)-3-nitrophenyl]acrylic acid methyl ester *N*-oxide (3d). This compound was prepared using the same procedure as for the preparation of **3a**: yield 68%; mp 135-137 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.12 (1H, s), 7.68 (1H, d, *J* = 16.0 Hz), 7.52 (1H, d, *J* = 8.7 Hz), 7.02 (1H, d, *J* = 8.7 Hz), 6.32

(1H, d, *J* = 16.0 Hz), 4.64 (2H, t, *J* = 4.2 Hz), 3.82 (3H, s), 3.79 (2H, t, *J* = 4.2 Hz), 3.40 (6H, s); ^{13}C-NMR ($CDCl_3$) δ: 169.0, 160.4, 151.2, 145.6, 134.5, 121.1, 120.2, 115.3, 113.7, 72.1, 56.8, 50.1, 40.6; IR (KBr) cm^{-1}: 3422, 1700, 1604, 1529, 1250, 1190; HR-MS (ESI) Calcd for $C_{14}H_{19}N_2O_6$ $(M+H)^+$: 311.1243. Found: 311.1248; *Anal*. Calcd for C, 54.19; H, 5.85; N, 9.03. Found C, 54.24; H, 5.82; N, 9.11.

3-[3-Bromo-4-(2-dimethylaminoethoxy)-5-methoxyphenyl]acrylic acid methyl ester *N*-oxide (3e). This compound was prepared using the same procedure as for the preparation of **3a**: yield 65%; mp 126-128 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.65 (1H, d, *J* = 16.0 Hz), 7.32 (1H, s), 6.99 (1H, s), 6.31 (1H, d, *J* = 16.0 Hz), 4.67 (2H, t, *J* = 4.2 Hz), 3.82 (3H, s), 3.71 (2H, t, *J* = 4.2 Hz), 3.85 (3H, s), 3.41 (6H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.2, 157.2, 152.3, 145.3, 141.7, 125.1, 124.7, 116.3, 114.6, 75.1, 61.3, 57.0, 50.6, 42.0; IR (KBr) cm^{-1}: 3427, 1708, 1605, 1255, 1184; HR-MS (ESI) Calcd for $C_{15}H_{21}BrNO_5$ $(M+H)^+$: 374.0603. Found: 374.0610; *Anal*. Calcd for C, 58.15; H, 5.39; N, 3.74. Found C, 58.58; H, 5.51; N, 3.68.

General Procedure: preparation of 3-[4-(2-Methylaminoethoxy)phenyl]acrylic acid methyl ester (4a). To a stirred mixture of 265 mg (1.0 mmol) of 3-[4-(2-dimethylaminoethoxy)phenyl]acrylic acid methyl ester *N*-oxide (**3a**) in 95% ethanol (10 mL) was added portionwise selenium dioxide (166 mg, 1.5 mmol) for 10 min. The mixture was heated to reflux for 4 h under an atmosphere of nitrogen. Insoluble materials were filtered off and the filtrate was concentrated by evaporation under reduced pressure. The residue thus obtained was purified by column chromatography through a silica gel column, using a gradient elution method, with a mixture of dichloromethane and methanol, in ratios ranging from 20:1 to 10:1 by volume, as the elution, to give 183 mg of 3-[4-(2-methylaminoethoxy)phenyl]acrylic acid methyl ester (**4a**): yield 78%; mp 196-198 °C; ^{1}H-NMR (DMSO-d_6) δ: 7.60 (2H, d, *J* = 8.7 Hz), 7.54 (1H, d, *J* = 16.0 Hz), 6.91 (2H, d, *J* = 8.7 Hz), 6.42 (1H, d, *J* = 16.0 Hz), 4.02 (2H, t, *J* = 5.5 Hz), 3.64 (3H, s), 2.83 (2H, t, *J* = 5.5 Hz), 2.30 (3H, s); ^{13}C-NMR (DMSO-d_6) δ: 165.2, 157.4, 141.7, 127.0, 126.3, 118.2, 116.9, 75.3, 56.8, 57.3, 34.5; IR (KBr) cm^{-1}: 3443, 2945, 1700, 1603, 1255, 1169; HR-MS (ESI) Calcd for $C_{13}H_{18}NO_3$ $(M+H)^+$: 236.1287. Found: 236.1285; *Anal*. Calcd for C, 66.36; H, 7.28; N, 5.95. Found C,

66.69.; H, 7.18; N, 5.54.

3-[4-(2-Methylaminoethoxy)-3-methoxyphenyl]acrylic acid methyl ester (4b). This compound was prepared using the same procedure as for the preparation of **4a**: yield: 80%; mp 197-199 °C; ^{1}H-NMR (DMSO-d_6) δ: 7.55 (1H, d, J = 8.7 Hz), 7.52 (1H, s), 7.48 (1H, d, J = 16.0 Hz), 6.85 (1H, d, J = 8.7 Hz), 6.36 (1H, d, J = 16.0 Hz), 4.01 (2H, t, J = 5.5 Hz), 3.73 (3H, s), 3.64 (3H, s), 2.76 (2H, t, J = 5.5 Hz), 2.27 (3H, s); ^{13}C-NMR (DMSO-d_6) δ: 165.2, 157.4, 141.7, 127.0, 126.3, 118.2, 116.9, 75.3, 56.8, 57.3, 34.5; IR (KBr) cm^{-1}: 3441, 2946, 1702, 1600, 1251, 1171; HR-MS (ESI) Calcd for $C_{14}H_{20}NO_4$ $(M+H)^+$: 266.1392. Found: 266.1390; *Anal*. Calcd for C, 63.38; H, 7.22; N, 5.28. Found C, 63.45; H, 7.30; N, 5.36.

3-[3,5-Dimethoxy-4-(2-methylaminoethoxy)phenyl]acrylic acid methyl ester (4c). This compound was prepared using the same procedure as for the preparation of **4a**: yield: 83%; mp 197-200 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.56 (1H, d, J = 16.0 Hz), 7.50 (2H, s), 6.35 (1H, d, J = 16.0 Hz), 4.12 (2H, t, J = 5.5 Hz), 3.78 (3H, s), 3.73 (6H, s), 2.77 (2H, t, J = 5.5 Hz), 2.26 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 169.2, 155.5, 147.1, 132.7, 120.6, 115.5, 114.0, 72.7, 59.4, 57.7, 51.2, 41.5; IR (KBr) cm^{-1}: 3439, 2943, 1701, 1600, 1250, 1185; HR-MS (ESI) Calcd for $C_{15}H_{22}NO_5$ $(M+H)^+$: 296.1498. Found: 296.1492; *Anal*. Calcd for C, 61.00; H, 7.17; N, 4.74. Found C, 61.33; H, 7.06; N, 4.75.

3-[4-(2-Methylaminoethoxy)-3-nitrophenyl]acrylic acid methyl ester (4d). This compound was prepared using the same procedure as for the preparation of **4a**: yield: 65%; mp 200-203 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.12 (1H, s), 7.65 (1H, d, J = 16.0 Hz), 7.58 (1H, d, J = 8.7 Hz), 6.99 (1H, d, J = 8.7 Hz), 6.30 (1H, d, J = 16.0 Hz), 4.13 (2H, t, J = 5.5 Hz), 3.81 (3H, s), 2.88 (2H, t, J = 5.5 Hz), 2.50 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.3, 160.2, 153.2, 141.1, 133.5, 118.6, 113.2, 113.0, 111.7, 72.5, 52.3, 50.5, 37.2; IR (KBr) cm^{-1}: 3440, 1704, 1604, 1527, 1251, 1177; HR-MS (ESI) Calcd for $C_{13}H_{17}N_2O_5$ $(M+H)^+$: 281.1137. Found: 281.1141; *Anal*. Calcd for C, 55.71; H, 5.75; N, 9.99. Found C, 55.42; H, 5.69; N, 9.83.

3-[3-Bromo-4-(2-dimethylaminoethoxy)-5-methoxyphenyl]acrylic acid methyl ester (4e). This compound was prepared using the same procedure as for the preparation of **4a**: yield: 70%; mp 197-199 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.62 (1H, d, *J* = 16.0 Hz), 7.29 (1H, s), 6.98 (1H, s), 6.27 (1H, d, *J* = 16.0 Hz), 4.06 (2H, t, *J* = 5.5 Hz), 3.80 (3H, s), 3.77 (3H, s), 2.88 (2H, t, *J* = 5.5 Hz), 2.21 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 166.9, 153.6, 150.2, 141.3, 129.4, 122.9, 118.7, 116.3, 114.6, 75.1, 61.3, 57.6, 49.8, 38.6; IR (KBr) cm^{-1}: 3441, 1700, 1602, 1249, 1175; HR-MS (ESI) Calcd for $C_{14}H_{19}BrNO_4$ $(M+H)^+$: 344.0497. Found: 344.0491; *Anal*. Calcd for C, 48.85; H, 5.27; N, 4.07. Found C, 48.56; H, 5.20; N, 4.11.

General Procedure: Preparation of 3-[4-(2-Dimethylaminoethoxy)phenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester *N*-oxide (6a). To a mixture of 3-[4-(2-dimethylaminoethoxy)phenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (**5a**) (499 mg, 1.0 mmol) in 10 mL of acetone was added dropwise 3.77 mL (40 mmol) of 30% hydrogen peroxide solution for 30 min at room temperature, and the resulting mixture was stirred at the same temperature for 8 h. The reaction mixture was concentrated by evaporation under reduced pressure. The concentrate thus obtained was purified by column chromatography through a silica gel column, using a gradient elution method, with a mixture of dichloromethane and methanol, in ratios ranging from 10:1 to 8:1 by volume, as the eluent, to give 412 mg of 3-[4-(2-dimethylamino-ethoxy)-phenyl]-acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester *N*-oxide (**6a**) as a white solid: yield 80%; mp 76-78 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.58 (1H, d, *J* = 16.0 Hz), 7.45 (2H, d, *J* = 8.6 Hz), 6.89 (2H, d, *J* = 8.6 Hz), 6.35 (1H, d, *J* = 16.0 Hz), 5.72 (1H, m), 5.19 (1H, t, *J* = 7.4 Hz), 4.57 (2H, m), 3.95 (2H, m), 3.67 (1H, dd, *J* = 2.5, 11.1 Hz), 3.45 (6H, s), 3.42 (3H, s), 2.98 (1H, d, *J* = 4.1 Hz), 2.60 (1H, t, *J* = 6.3 Hz), 2.55 (1H, d, *J* = 4.1 Hz), 2.33 (1H, m), 2.14 (2H, m), 2.02 (2H, m), 1.87 (1H, m), 1.70 (3H, s), 1.63 (3H, s), 1.19 (3H, s), 1.07 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 166.7, 159.2, 144.2, 134.9, 129.9, 128.1, 118.6, 116.6, 114.9, 79.3, 69.7, 66.4, 62.2, 61.1, 59.8, 59.7, 59.5, 58.6, 56.7, 50.9, 48.3, 29.4, 27.4, 25.7, 18.0, 13.9; IR (KBr) cm^{-1}: 3447, 2925, 1706, 1603, 1251, 1171; HR-MS (ESI) Calcd for $C_{29}H_{42}NO_7$ $(M+H)^+$: 516.2961. Found: 516.2963;

Anal. Calcd for C, 67.55; H, 8.01; N, 2.72. Found C, 67.15.; H, 7.88; N, 2.74.

3-[4-(2-Dimethylaminoethoxy)-3-methoxyphenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester *N*-oxide (6b). This compound was prepared using the same procedure as for the preparation of **6a**: yield 76%; mp 77-79 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.56 (1H, d, *J* = 16.0 Hz), 7.51 (1H, d, *J* = 8.6 Hz), 7.49 (1H, s), 6.86 (1H, d, *J* = 8.6 Hz), 6.33 (1H, d, *J* = 16.0 Hz), 5.71 (1H, m), 5.20 (1H, t, *J* = 7.4 Hz), 4.65 (2H, m), 3.99 (2H, m), 3.68 (1H, dd, *J* = 2.5, 11.1 Hz), 3.47 (6H, s), 3.43 (3H, s), 3.38 (3H, s), 2.97 (1H, d, *J* = 4.1 Hz), 2.57 (1H, t, *J* = 6.3 Hz), 2.55 (1H, d, *J* = 4.1 Hz), 2.30 (1H, m), 2.13 (2H, m), 2.08 (2H, m), 1.90 (1H, m), 1.70 (3H, s), 1.64 (3H, s), 1.21 (3H, s), 1.05 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 166.8, 159.7, 145.0, 135.2, 129.7, 128.2, 119.0, 116.9, 114.7, 79.4, 69.7, 67.1, 66.9, 63.0, 61.8, 59.4, 59.0, 58.9, 58.7, 56.6, 51.0, 48.5, 29.9, 27.1, 26.0, 18.1, 14.3; IR (KBr) cm^{-1}: 3446, 2925, 1705, 1600, 1252, 1170; HR-MS (ESI) Calcd for $C_{30}H_{44}NO_8$ $(M+H)^+$: 546.3067. Found: 546.3062; *Anal*. Calcd for C, 66.03; H, 7.94; N, 2.57. Found C, 66.35; H, 7.97; N, 2.51.

3-[4-(2-Dimethylaminoethoxy)-3,5-dimethoxyphenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester *N*-oxide (6c). This compound was prepared using the same procedure as for the preparation of **6a**: yield 72%; mp 79-81 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.52 (1H, d, *J* = 16.0 Hz), 7.38 (2H, s), 6.39 (1H, d, *J* = 16.0 Hz), 5.68 (1H, m), 5.21 (1H, t, *J* = 7.4 Hz), 4.58 (2H, m), 3.93 (2H, m), 3.66 (1H, dd, *J* = 2.5, 11.1 Hz), 3.44 (6H, s), 3.39 (6H, s), 3.36 (3H, s), 2.86 (1H, d, *J* = 4.1 Hz), 2.59 (1H, t, *J* = 6.3 Hz), 2.57 (1H, d, *J* = 4.1 Hz), 2.30 (1H, m), 2.14 (2H, m), 2.10 (2H, m), 1.82 (1H, m), 1.71 (3H, s), 1.65 (3H, s), 1.20 (3H, s), 1.04 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 165.9, 157.0, 136.2, 128.4, 119.5, 115.3, 112.2, 79.1, 64.1, 63.9, 62.4, 61.9, 61.4, 57.3, 57.2, 56.2, 56.0, 55.4, 51.2, 48.8, 30.1, 26.8, 26.1, 18.6, 14.2; IR (KBr) cm^{-1}: 3445, 2923, 1701, 1600, 1251, 1169; HR-MS (ESI) Calcd for $C_{31}H_{46}NO_9$ $(M+H)^+$: 576.3173. Found: 576.3177; *Anal*. Calcd for C, 64.68; H, 7.88; N, 2.43. Found C, 64.33; H, 7.82; N, 2.47.

3-[4-(2-Dimethylaminoethoxy)-3-nitrophenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester *N*-oxide (6d). This compound was prepared using the same procedure as for the preparation of **6a**: yield 63%; mp 80-82 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.15 (1H, s), 7.61 (1H, d, *J* = 16.0 Hz), 7.38 (1H, d, *J* = 8.6 Hz), 6.99 (1H, d, *J* = 8.6 Hz), 6.27 (1H, d, *J* = 16.0 Hz), 5.65 (1H, m), 5.23 (1H, t, *J* = 7.4 Hz), 4.59 (2H, m), 3.91 (2H, m), 3.67 (1H, dd, *J* = 2.5, 11.1 Hz), 3.46 (6H, s), 3.41 (3H, s), 2.96 (1H, d, *J* = 4.1 Hz), 2.54 (1H, t, *J* = 6.3 Hz), 2.53 (1H, d, *J* = 4.1 Hz), 2.30 (1H, m), 2.12 (2H, m), 2.08 (2H, m), 1.91 (1H, m), 1.73 (3H, s), 1.67 (3H, s), 1.22 (3H, s), 1.04 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 165.9, 159.9, 140.0, 134.7, 128.1 127.3, 117.7, 117.0, 114.5, 80.1, 68.7, 66.9, 66.5, 62.4, 61.5, 59.6, 59.1, 57.1, 56.6, 51.5, 48.0, 29.6, 27.4, 25.5, 18.4, 13.6; IR (KBr) cm^{-1}: 3445, 2927, 1703, 1601, 1251, 1171; HR-MS (ESI) Calcd for $C_{29}H_{41}N_2O_9$ $(M+H)^+$: 561.2812. Found: 561.2819; *Anal*. Calcd for C, 62.13; H, 7.19; N, 5.00. Found C, 61.99; H, 7.11; N, 5.29.

3-[3-Bromo-4-(2-dimethylaminoethoxy)-5-methoxyphenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester *N*-oxide (6e). This compound was prepared using the same procedure as for the preparation of **6a**: yield 60%; mp 76-78 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.61 (1H, d, *J* = 16.0 Hz), 7.49 (1H, s), 6.91 (1H, s), 6.27 (1H, d, *J* = 16.0 Hz), 5.59 (1H, m), 5.24 (1H, t, *J* = 7.4 Hz), 4.54 (2H, m), 3.98 (2H, m), 3.67 (1H, dd, *J* = 2.5, 11.1 Hz), 3.39 (6H, s), 3.41 (3H, s), 3.34 (3H, s), 2.80 (1H, d, *J* = 4.1 Hz), 2.51 (1H, t, *J* = 6.3 Hz), 2.56 (1H, d, *J* = 4.1 Hz), 2.27 (1H, m), 2.15 (2H, m), 2.09 (2H, m), 1.92 (1H, m), 1.71 (3H, s), 1.65 (3H, s), 1.19 (3H, s), 1.03 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 165.2, 158.3, 144.4, 135.7, 128.9, 128.2, 119.2, 116.1, 115.3, 76.1, 69.5, 67.3, 65.0, 63.4, 61.8, 59.6, 58.9, 58.7, 58.0, 56.0, 50.7, 48.5, 28.6, 27.1, 26.4, 18.6, 13.7; IR (KBr) cm^{-1}: 3441, 2920, 1702, 1603, 1249, 1170; HR-MS (ESI) Calcd for $C_{30}H_{43}BrNO_8$ $(M+H)^+$: 624.2172. Found: 624.2179; *Anal*. Calcd for C, 57.69; H, 6.78; N, 2.24. Found C, 57.98; H, 6.51; N, 2.25.

General Procedure: Preparation of 3-[4-(2-Methylaminoethoxy)phenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (7a). To a stirred mixture of 515

mg (1.0 mmol) of 3-[4-(2-dimethylaminoethoxy)phenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester *N*-oxide (**6a**) in 95% ethanol (10 mL) was added selenium dioxide (1.66 mg, 1.5 mmol). The rmixture was heated to reflux for 4 h under an atmosphere of nitrogen. Insoluble materials were filtered away and the filtrate was concentrated by evaporation under reduced pressure. The residue thus obtained was purified by column chromatography through a silica gel column, using a gradient elution method, with a mixture of dichloromethane and methanol, in ratios ranging from 10:1 to 8:1 by volume, as the elution, to give 373 mg of 3-[4-(2-methylamino-ethoxy)-phenyl]-acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (**7a**): yield 77%; mp 143-145 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.60 (1H, d, *J* = 16.0 Hz), 7.45 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 6.33 (1H, d, *J* = 16.0 Hz), 5.72 (1H, m), 5.20 (2H, m), 4.12 (1H, m), 3.68 (1H, dd, *J* = 11.1, 2.8 Hz), 3.43 (3H, s), 2.99 (3H, m), 2.62-2.51 (5H, m), 2.33 (1H, m), 2.16-1.99 (4H, m), 1.85 (1H, m), 1.73 (3H, s), 1.50 (3H, s), 1.21 (3H, s), 1.10 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 166.7, 159.1, 144.0, 135.0, 129.8, 128.2, 118.3, 116.6, 115.2, 79.5, 69.9, 62.4, 59.9, 59.5, 59.4, 58.3, 56.5, 51.0, 49.6, 48.3, 29.8, 27.6, 26.1, 18.4, 13.6; IR (KBr) cm^{-1}: 3449, 2928, 1707, 1603, 1251, 1169; HR-MS (ESI) Calcd for $C_{28}H_{40}NO_6$ $(M+H)^+$: 4863.2856. Found: 486.2857; *Anal*. Calcd for C, 69.25; H, 8.09; N, 2.88. Found C, 69.33.; H, 8.12; N, 2.85.

3-[3-Methoxy-4-(2-methylaminoethoxy)phenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (7b). This compound was prepared using the same procedure as for the preparation of **7a**: yield 82%; mp 144-146 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.58 (1H, d, *J* = 16.0 Hz), 7.41 (1H, d, *J* = 8.7 Hz), 7.35 (1H, s), 6.83 (1H, d, *J* = 8.7 Hz), 6.23 (1H, d, *J* = 16.0 Hz), 5.70 (1H, m), 5.24 (2H, m), 4.12 (1H, m), 3.71 (3H, s), 3.66 (1H, dd, *J* = 11.1, 2.8 Hz), 3.43 (3H, s), 3.01 (3H, m), 2.59-2.48 (5H, m), 2.30 (1H, m), 2.17-2.00 (4H, m), 1.85 (1H, m), 1.72 (3H, s), 1.51 (3H, s), 1.20 (3H, s), 1.08 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 166.3, 159.1, 145.2, 134.9, 129.0, 128.4, 119.1, 117.1, 114.8, 80.1, 70.1, 63.4, 62.3, 59.5, 59.2, 58.9, 58.8, 55.3, 51.2, 48.5, 48.1, 29.7, 27.0, 25.8, 17.7, 13.9; IR (KBr) cm^{-1}: 3445, 2929, 1706, 1600, 1251, 1171; HR-MS (ESI) Calcd for $C_{29}H_{42}NO_7$ $(M+H)^+$: 516.2961. Found: 516.2967; *Anal*. Calcd for C, 67.55; H, 8.01; N, 2.72. Found C, 67.96.; H, 7.88; N, 2.70.

3-[3,5-Dimethoxy-4-(2-methylaminoethoxy)phenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (7c). This compound was prepared using the same procedure as for the preparation of **7a**: yield 85%; mp 146-148 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.57 (1H, d, *J* = 16.0 Hz), 7.36 (2H, s), 6.27 (1H, d, *J* = 16.0 Hz), 5.74(1H, m), 5.20 (2H, m), 4.16 (1H, m), 3.71 (6H, s), 3.55 (1H, dd, *J* = 11.1, 2.8 Hz), 3.41 (3H, s), 2.99 (3H, m), 2.57-2.45 (5H, m), 2.26 (1H, m), 2.17-2.03 (4H, m), 1.81 (1H, m), 1.75 (3H, s), 1.50 (3H, s), 1.18 (3H, s), 1.04 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 165.3, 158.8, 133.9, 126.5, 118.1, 117.4, 114.0, 79.6, 70.1, 63.1, 62.0, 59.8, 59.6, 58.7, 58.4, 54.1, 50.7, 48.5, 48.2, 29.3, 27.7, 26.4, 17.3, 13.2; IR (KBr) cm^{-1}: 3446, 2925, 1700, 1602, 1250, 1169; HR-MS (ESI) Calcd for $C_{30}H_{43}NO_8$ $(M+H)^+$: 545.2989. Found: 545.2980; *Anal*. Calcd for C, 65.91; H, 8.11; N, 2.56. Found C, 65.80; H, 8.32; N, 2.49.

3-[4-(2-Methylaminoethoxy)-3-nitrophenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (7d). This compound was prepared using the same procedure as for the preparation of **7a**: yield 62%; mp. 147-150 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.12 (1H, s), 7.60 (1H, d, *J* = 16.0 Hz), 7.36 (1H, d, *J* = 8.7 Hz), 6.91 (1H, d, *J* = 8.7 Hz), 6.26 (1H, d, *J* = 16.0 Hz), 5.71 (1H, m), 5.22 (2H, m), 4.24 (1H, m), 3.66 (1H, dd, *J* = 11.1, 2.8 Hz), 3.40 (3H, s), 2.88 (3H, m), 2.51-2.43 (5H, m), 2.37 (1H, m), 2.19-2.02 (4H, m), 1.88 (1H, m), 1.67 (3H, s), 1.55 (3H, s), 1.23 (3H, s), 1.13 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 167.0, 158.3, 145.5, 135.9, 128.6, 128.4, 119.0, 115.1, 114.8, 80.1, 67.8, 65.2, 61.3, 59.7, 59.0, 58.5, 58.7, 55.1, 50.9, 48.7, 47.1, 28.4, 27.1, 25.6, 15.7, 13.0; IR (KBr) cm^{-1}: 3446, 2924, 1702, 1603, 1250, 1169; HR-MS (ESI) Calcd for $C_{28}H_{43}NO_8$ $(M+H)^+$: 531.2706. Found: 531.2701; *Anal*. Calcd for C, 63.38; H, 7.22; N, 5.28. Found C, 63.16.; H, 7.30; N, 5.33.

3-[3-Bromo-5-methoxy-4-(2-methylaminoethoxy)phenyl]acrylic acid 5-methoxy-4-[2-methyl-3-(3-methylbut-2-enyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester (7e). This compound was prepared using the same procedure as for the preparation of **7a**: yield 65%; mp. 144-146 °C; ^{1}H-NMR ($CDCl_3$) δ: 7.61 (1H, d, *J* = 16.0 Hz), 7.41 (1H, s), 6.91 (1H, s), 6.24 (1H, d, *J* = 16.0 Hz), 5.64 (1H, m), 5.29 (2H, m), 4.17

(1H, m), 3.67 (3H, s), 3.58 (1H, dd, *J* = 11.1, 2.8 Hz), 3.39 (3H, s), 3.02 (3H, m), 2.57-2.46 (5H, m), 2.28 (1H, m), 2.20-2.03 (4H, m), 1.84 (1H, m), 1.70 (3H, s), 1.49 (3H, s), 1.19 (3H, s), 1.06 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 164.9, 156.2, 144.3, 135.9, 128.7, 127.6, 120.4, 117.1, 114.5, 79.1, 71.1, 63.3, 61.3, 59.0, 58.9, 58.7, 58.6, 54.9, 51.8, 47.5, 48.2, 29.0, 27.7, 25.5, 17.1, 13.2; IR (KBr) cm^{-1}: 3443, 2924, 1704, 1605, 1252, 1170; HR-MS (ESI) Calcd for $C_{29}H_{41}BrNO_7$ $(M+H)^+$: 594.2066. Found: 594.2070; *Anal*. Calcd for C, 58.59; H, 6.78; N, 2.36. Found C, 58.21.; H, 6.90; N, 2.33.

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