CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.200600199

Enantio- and Diastereoselective Total Synthesis of (+)-Panepophenanthrin, a Ubiquitin-Activating Enzyme Inhibitor, and Biological Properties of Its New Derivatives

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Abstract: The asymmetric total synthesis of (+)-panepophenanthrin, an inhibitor of ubiquitin-activating enzyme (E1), has been accomplished using catalytic asymmetric α aminoxylation of 1,4-cyclohexanedione monoethylene ketal as a key step, followed by several diastereoselective reactions. The biomimetic Diels–Alder reaction of a monomer precursor was found to proceed efficiently in water. The investigation of the biological properties of new derivatives of (+)-panepophenanthrin enabled us to develop new cell-permeable E1 inhibitors, RKTS-80, -81, and -82.

Keywords: asymmetric synthesis · chemical biology · natural products · panepophenanthrin · total synthesis

Introduction

Panepophenanthrin (**1**) is a natural product that inhibits ubiquitin-activating enzyme (E1) and was isolated by Sekizawa and co-workers in 2002 from the mushroom strain *Panus rudis* Fr. IFO8994.[1] As ubiquitin-activating enzyme (E1) plays an important role in the ubiquitin-proteasome pathway (UPP), which regulates a variety of important cellular processes by degradation or processing of target proteins, an inhibitor of ubiquitin-activating enzyme (E1) would be a promising drug candidate for cancers, inflammation, and neurodegenerative disease.[2] Structurally, panepophenanthrin has a complex architecture with a highly substituted tetracyclic skeleton, which contains 11 contiguous stereocenters. Panepophenanthrin belongs to the so-called epoxyquinoid natural-product family, whose members are synthesized by Diels–Alder dimerization of much simpler epoxyquinol monomers.[3] Its synthetically challenging structure along with its important biological activity make panepophenanthrin an attractive synthetic target. In fact, since its isolation in 2002, three groups have already accomplished its total synthesis. Porco and co-workers reported the first asymmetric total synthesis through biomimetic Diels–Alder dimerization of a monomer, synthesized by diisopropyl tartrate mediated asymmetric epoxidation, in which excess amounts (1.6 equiv) of a chiral controller were employed.[4] They clearly explained the reaction mechanism of the Diels–Alder dimerization. Baldwin and co-workers[5] accomplished its total synthesis in racemic form from the known (±)-bromoxone in three steps; enantiomerically pure (−)-bromoxone is known to be prepared by enzymatic resolution,[6] giving the formal total synthesis of the chiral panepophenanthrin. Mehta and co-workers synthesized (+)-panepophenanthrin by using lipase-mediated enzymatic desymmetrization as a key step,[7a] and the (−) isomer was synthesized through lipase-mediated enzymatic resolution by the same group.[7b] Although these are excellent syntheses, no asymmetric catalytic method has been reported. The preparation of chiral (+)-panepophenanthrin and its derivatives in a practical and atom-economical manner is desirable for biological investigations.

Our group has been involved in the chemistry and biology of epoxyquinol dimers such as epoxyquinol A, B, C, and epoxytwinol A, novel angiogenesis inhibitors,[8] epoxyquinol

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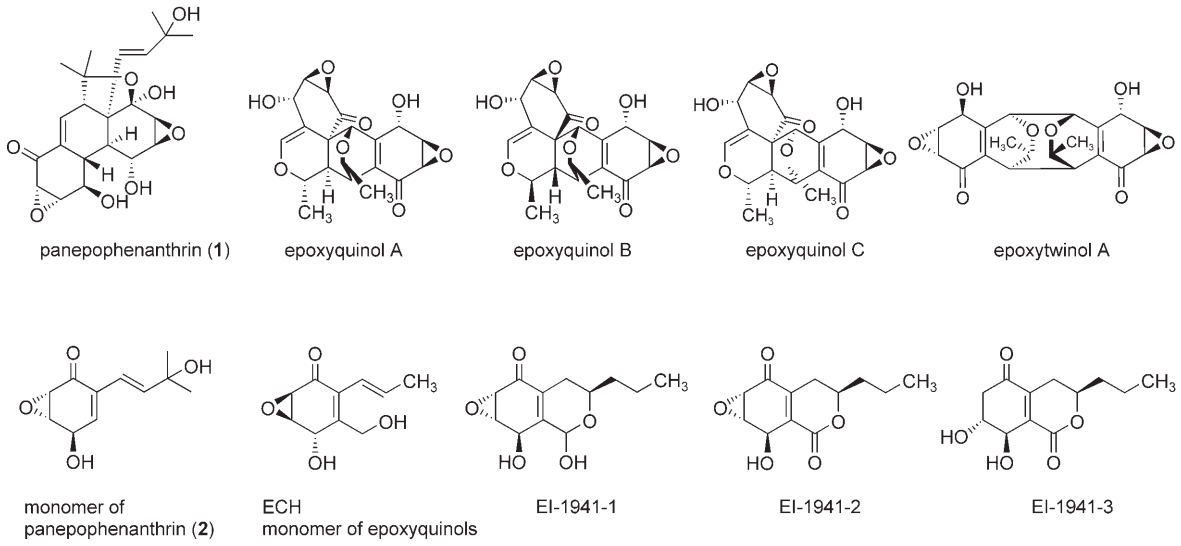


monomers such as ECH, an inhibitor of FasL-induced apoptosis,[9] and EI-1941-1, -2, and -3, inhibitors of interleukin-1β-converting enzymes.[10] Being interested in its complex structure and important biological activity, we have examined the asymmetric total synthesis of (+)-panepophenanthrin. Although there is a similarity between the monomers of panepophenanthrin and of the epoxyquinols, we have developed a completely different synthetic route from that of our previous synthesis of the epoxyquinols, in which a $HfCl_4$-mediated diastereoselective Diels–Alder reaction of furan[11] and a Diels–Alder reaction of furan with acryloyl chloride as a reactive dienophile, followed by lipase-mediated kinetic resolution, were developed as key steps. The present synthetic route is based on a practical, asymmetric catalytic reaction, which is also completely different from those of the previous three groups.

We have been developing proline-mediated asymmetric catalytic α aminoxylation of carbonyl compounds,[12] which is a powerful method for the synthesis of α-hydroxy carbonyl derivatives. Employing this reaction as a key step and with several diastereoselective transformations, we have accomplished the asymmetric total synthesis of panepophenanthrin, which we disclose herein. On the basis of this established synthetic route, several new derivatives were prepared, and their biological properties were evaluated, which we also discuss.

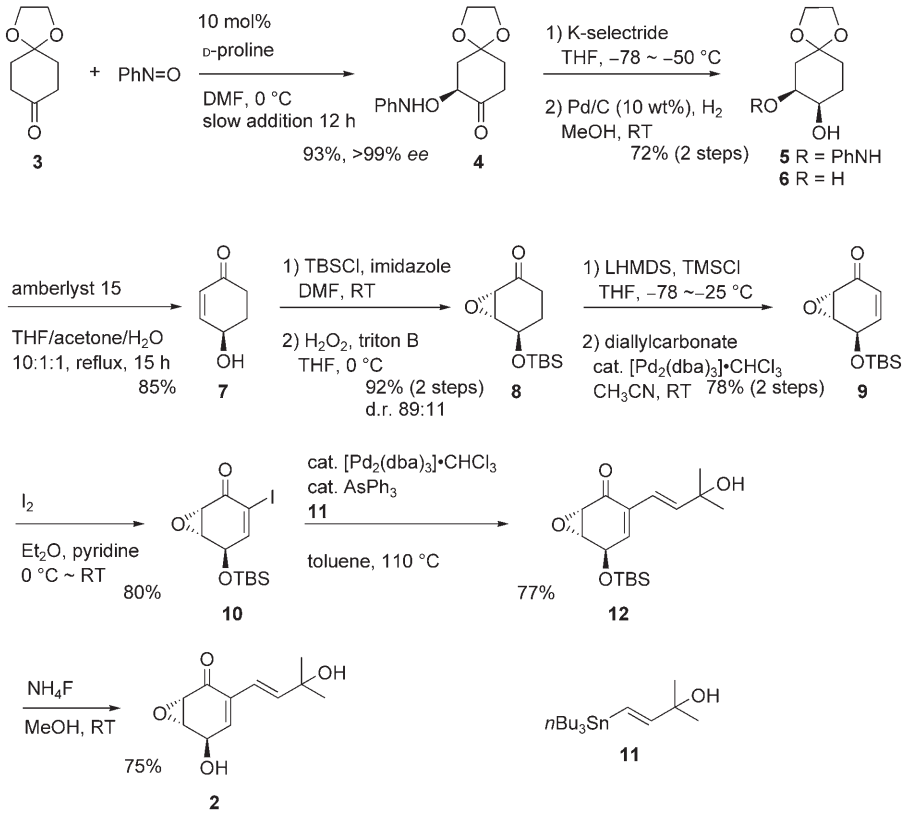
Abstract in Japanese:

1,4-シクロヘキサンジオンモノエチレンケタール (**3**)に対するプロリンを触媒としたα-アミノオキシ化反応を鍵反応とし、ユビキチン活性化酵素(E1)阻害作用を有する(+)-panepophenanthrin の不斉全合成、および新規類縁化合物の合成を達成した。また、生合成を模倣したモノマー**2**のディールス•アルダー反応が水中においても速やかに進行することを見いだした。さらに、生物活性評価の結果、細胞膜透過性に優れた新規類縁化合物 RKTS-80 (**19**)、-81 (**20**)、-82 (**21**)を見出した。

Results and Discussion

Asymmetric Synthesis of (+)-Panepophenanthrin

The first reaction in our sequence, α aminoxylation of 1,4-cyclohexanedione monoethylene ketal (**3**) (1.2 equiv) in the presence of D-proline (10 mol%) with slow addition of nitrosobenzene (1.0 equiv) over 24 h proceeded efficiently at 0°C to afford nearly optically pure (*S*)-α-aminoxylated cyclohexanone **4** (>99% *ee*) in 93% yield (Scheme 1). This reaction can be carried out on a large scale to generate 25 g of **4** without compromising yield or enantioselectivity.[12a,b] The (*R*)-α-aminoxylated cyclohexanone, the enantiomer of **4**, has been converted successfully into the fumagillin and ovalicin families by several diastereoselective reactions.[13] The reduction of cyclohexanone **4** with K-selectride proceeded stereoselectively to afford the alcohol *cis*-**5**. In this reduction, the *trans* isomer was not detected. Reductive cleavage of the N–O bond in the presence of Pd/C under a H_2 atmosphere gave the diol *cis*-**6** in 72% yield over two steps. Treatment of **6** with amberlyst in THF/acetone/water at reflux removed the acetal protecting group and resulted in a dehydration reaction to provide 4-hydroxycyclohex-2-enone (**7**) in 85% yield. Enone **7** is an intermediate in the synthesis of (+)-epiepoformin, (+)-epiepoxydon, and (+)-bromoxone by Kitahara and Tachihara.[14] The hydroxy group was protected by using *tert*-butyldimethylchlorosilane and imidazole. Epoxidation with H_2O_2 and triton B by following the protocol of Kitahara and Tachihara[14] gave epoxide **8** stereoselectively. Cyclohexanone **8** was converted into the corresponding cyclohexenone **9** in a two-step procedure in 78% yield:



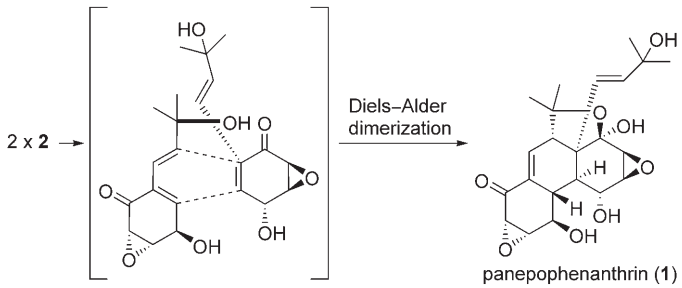
Scheme 1. Synthesis of the monomer of panepophenanthrin (**1**). DMF = *N*,*N*-dimethylformamide, TBS = *tert*-butyldimethylsilyl, LHMDS = lithium hexamethyldisilazide, dba = *trans*,*trans*-dibenzylideneacetone.

1) formation of silyl enol ether by reaction of **8** with lithium hexamethyldisilazide and trimethylsilylchloride; 2) treatment of the resultant enol ether with diallylcarbonate in the presence of $[Pd_2(dba)_3]\cdot CHCl_3$ under Tsuji's modified conditions[15] of the Saegusa reaction.[16] Introduction of iodine at C2 of cyclohexenone **9** by reaction with I_2 in a mixture of Et_2O and pyridine[17] gave **10** in 80% yield. Coupling of **10** and vinyl stannane **11** proceeded in the presence of a catalytic amount of $[Pd_2(dba)_3]\cdot CHCl_3$ and $AsPh_3$[18] at 110 °C in toluene to provide the coupled product **12** in 77% yield. Removal of the silyl protecting group by treatment with NH_4F in MeOH afforded monomer **2** in good yield.

It is already known that monomer **2** dimerizes by allowing it to stand at 25 °C in the absence of solvent (24 h, 80% yield) (Scheme 2).[4,5,7] Although panepophenanthrin was synthesized in good yield by this procedure in our hands, these reaction conditions, particularly the absence of solvent, would not be similar to those under which the reaction occurs in living cells. We therefore investigated the dimerization in water, which would be similar to biological conditions. The results are summarized in Figure 1 along with the results obtained with other solvents. Dimerization proceeded efficiently in the absence of solvent as described above, which gave the best result. Whereas the reaction proceeds slowly in MeOH and THF and affords the Diels–Alder product in low yield, the reaction in water is much faster than the reaction in organic solvents. That is, when monomer **2** (1 mg) was dissolved in D_2O (200 μL), the reaction proceeded efficiently to afford panepophenanthrin (**1**) in moderate yield after 33 h. Although Breslow and co-workers showed that some Diels–Alder reactions are faster in water than in organic solvents,[19] the present result, that panepophenanthrin is synthesized in a reasonable yield in water at room temperature, is a piece of evidence to support the supposition that the biosynthesis of panepophenanthrin occurs through a non-enzymatic Diels–Alder reaction in living cells.

Synthesis of New (+)-Panepophenanthrin Derivatives

With a practical synthetic route to (+)-panepophenanthrin in place, we next investigated the structure–activity relationships of some new derivatives. The effects of the side chain and



Scheme 2. Dimerization of monomer **2** through a Diels–Alder reaction to give panepophenanthrin (**1**).

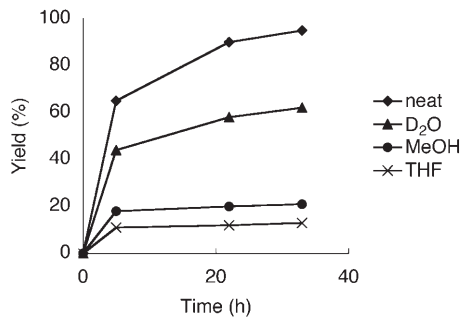
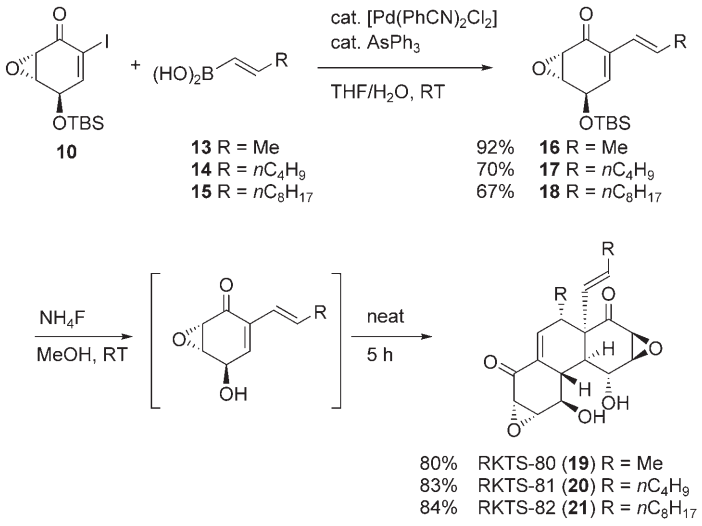


Figure 1. Effect of solvent and time on the yield of the Diels–Alder reaction of **2**.

ring systems of panepophenanthrin were examined. Monomers with propenyl, hexenyl, and decenyl substituents were synthesized from intermediate **10**. Suzuki coupling of **10** with alkenyl borates **13**, **14**, and **15** proceeded efficiently in the presence of $[Pd(PhCN)_2Cl_2]$ with $AsPh_3$ to provide dienes **16**, **17**, and **18**, respectively, in good yields (Scheme 3). The *tert*-butyldimethylsilyl group was removed



Scheme 3. Synthesis of new panepophenanthrin derivatives RKTS-80, -81, and -82.

by treatment with NH_4F in MeOH to afford the respective alcohols, which dimerized smoothly under neat reaction conditions to give Diels–Alder products RKTS-80 (**19**), RKTS-81 (**20**), and RKTS-82 (**21**), respectively, in good yield as single isomers. Porco and co-workers reported that the *tert*-hydroxy group in the side chain of **2** is not necessary for dimerization, and the same phenomenon was observed in the present derivatives. Once the derivatives were in hand, their biological activity was investigated.

Biological Properties of New (+)-Panepophenanthrin Derivatives

We evaluated the effects of new derivatives RKTS-80 (**19**), -81 (**20**), and -82 (**21**) on E1 activity in vitro. E1 catalyzes the formation of a ubiquitin adenylate intermediate from ubiquitin and ATP, and subsequently the binding of ubiquitin to a cysteine residue in the E1 active site in a thiol ester linkage. E1 activity, therefore, was analyzed by detecting the formation of the E1–ubiquitin intermediate from recombinant E1 and biotinylated ubiquitin in the presence of ATP (Figure 2). The ubiquitylated E1 was observed as the spot at approximately 120 kDa in this assay system. RKTS-80, -81, and -82 inhibited the formation of the E1–ubiquitin intermediate in a dose-dependent manner. The IC_{50} values of RKTS-80, -81, and -82 were 9.4, 3.5, and 90 μM, respectively, quantified by densitometric analysis. Our synthetic (+)-pan-

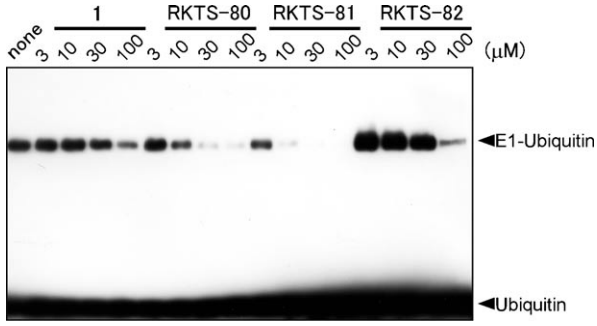


Figure 2. Inhibition of the E1–ubiquitin intermediate formation by (+)-panepophenanthrin (**1**) and new derivatives (RKTS-80, -81, and -82). Recombinant yeast E1, biotinylated ubiquitin, and ATP were incubated in the absence or presence of **1**, RKTS-80, -81, or -82 at various concentrations. The reaction mixture was then subjected to SDS-PAGE, and the biotin moiety was detected by the chemiluminescence method. The bands of E1–ubiquitin and ubiquitin represent the ubiquitylated E1 and the free biotinylated ubiquitin.

epophenanthrin (**1**) also blocked the E1–ubiquitin intermediate with an IC_{50} value of 72 μM. These results indicate that the 2,2-dimethyltetrahydrofuran moiety in **1** is not always necessary to inhibit the formation of the E1–ubiquitin intermediate. We then tested the effects of these compounds on the growth of human breast cancer MCF-7 cells[9,20] (Figure 3). RKTS-80, -81, and -82 blocked cell

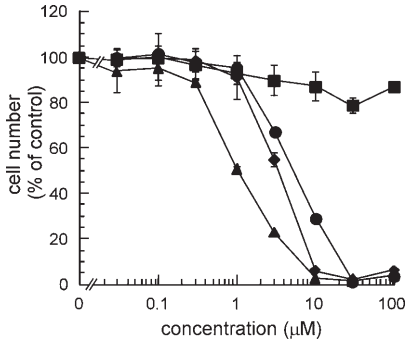


Figure 3. Effects of (+)-panepophenanthrin (**1**) and new derivatives (RKTS-80, -81, and -82) on the cell growth of MCF-7 cells. MCF-7 cells were cultured in RPMI-1640 cells containing 10% fetal bovine serum for 48 h in the presence of **1** (■), RKTS-80 (●), RKTS-81 (▲), or RKTS-82 (◆) at various concentrations at 37°C in a 5% humidified atmosphere. The cell number was evaluated by WST-8.

growth in a dose-dependent manner; IC_{50} values of RKTS-80, -81, and -82 were 5.4, 1.0, and 3.6 μM, respectively. The potency trend in the inhibition of cell growth is different from that in E1 inhibitory activity in vitro. These results might be caused by the difference in membrane permeability as well as the other mechanisms besides E1 inhibition by these compounds. On the other hand, synthetic (+)-panepophenanthrin (**1**) was unable to inhibit cell growth, even at 100 μM, suggesting that **1** might exhibit poor membrane permeability.

Conclusions

We have completed an enantio- and diastereoselective total synthesis of (+)-panepophenanthrin by the proline-mediated α aminoxylation of 1,4-cyclohexanedione monoethylene ketal followed by stereoselective reactions. Diels–Alder dimerization was found to proceed faster in water than in organic solvent. The investigation of the biological properties of its derivatives in vitro and in vivo showed that the new derivatives RKTS-80, -81, and -82 are effective cell-permeable E1 inhibitors.

Experimental Section

General Methods

All reactions were carried out under an argon atmosphere and monitored by thin-layer chromatography with Merck 60 F_{254} precoated silica gel plates (0.25-mm thickness). Specific optical rotations were measured with a JASCO P-1020 polarimeter. FTIR spectra were recorded on a Horiba FT-720 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 instrument. High-resolution mass spectral analysis (HRMS) was carried out on a JEOL JMSSX 102A. Preparative thin-layer chromatography was performed with Merck Silica Gel 60 F_{254} and Wakogel B-5F purchased from Wako Pure Chemical Industries, Japan. Flash chromatography was carried out with Silica Gel Merck Art 7734 and silica gel 60N of Kanto Chemical Co. Int., Tokyo, Japan.

4: A solution of nitrosobenzene (13.7 g, 127.9 mmol) in DMF (150 mL) was added through a syringe pump to a solution of 1,4-dioxaspiro-[4.5]decan-8-one (**3**) (20.0 g, 128.1 mmol) and D-proline (1.5 g, 12.7 mmol) in DMF (250 mL) over 24 h at 0 °C, and the mixture was stirred for 30 min at that temperature. The reaction was quenched with pH 7.0 phosphate buffer solution, the organic materials were extracted with ethyl acetate (3×100 mL), the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by silica-gel column chromatography (hexane/EtOAc = 10:1–4:1) gave (*S*)-7-Anilinoxy-1,4-dioxaspiro-[4.5]decan-8-one (**4**) (31.4 g, 119.1 mmol, 93 %) as a pearl-yellow solid. $[\alpha]_D^{18} = -78.7$ ($c = 1.2$, $CHCl_3$), >99 % *ee* (the enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (hexane/2-propanol 10:1), 0.5 mL min^{-1}; major enantiomer $t_r = 29.1$ min, minor enantiomer $t_r = 26.5$ min); IR (KBr): $\tilde{\nu} = 2960$, 2888, 1728, 1602, 1494, 1305, 1122, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 1.88$–2.04 (2H, m), 2.16 (1H, t, J = 12.8 Hz), 2.36–2.46 (2H, m), 2.62 (1H, dt, $J = 14.0$, 6.8 Hz), 4.38–4.21 (4H, m), 4.60 (1H, dd, $J = 12.9$, 6.5 Hz), 6.87 (2H, d, $J = 7.7$ Hz), 6.90 (1H, t, $J = 7.2$ Hz), 7.20 ppm (2H, t, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ = 34.9, 36.0, 39.7, 64.8, 64.9, 82.7, 107.6, 114.5, 122.2, 128.9, 148.0, 208.6 ppm; HRMS (FAB): calcd for $C_{14}H_{17}NO_4$: 263.1158, found: 263.1172.

6: A solution of K-selectride in THF (1 M, 23.1 mL, 23.1 mmol) was added to a solution of α-aminoxy ketone **4** (3.0 g, 12.0 mmol) in THF (77 mL) at −78 °C, and the reaction temperature was increased to −50 °C over 1.5 h. $NaBO_3$ (10.8 g, 0.0701 mmol) and H_2O (23 mL) were added to the reaction mixture, and stirring was continued for 2 h at room temperature. The two phases were separated, and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with brine and dried over $MgSO_4$. The organic phase was concentrated in vacuo to give the alcohol **5** (4.6 g), which was used directly in the next reaction without purification. Pd/C (10 wt %; 304 mg, 0.29 mmol) was added to a solution of the crude alcohol **5** MeOH (38 mL). The reaction mixture was stirred under H_2 for 3 h at room temperature. Inorganic materials were removed by filtration through a celite pad, and the filtrate was concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 3:1–1:3) to afford (7*S*,8*S*)-1,4-dioxaspiro[4.5]decane-7,8-diol (**6**) (1.7 g, 9.8 mmol, 85 %) as a dark-red oil. $[\alpha]_D^{21} = +2.6$ ($c = 1.5$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3417$, 2958, 2935, 2888, 1442, 1144, 1101, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.40$–1.50 (1H, m), 1.60–1.80 (4H, m), 1.80–1.90 (1H, m), 3.20 (1H, s), 3.54 (1H, s), 3.67 (1H, s), 3.79 (1H, s), 3.82–3.88 ppm (4H, m); ^{13}C NMR ($CDCl_3$): δ = 26.5, 30.1, 37.5, 64.0, 64.2, 69.1, 70.0, 108.6 ppm; HRMS (FAB): calcd for $C_8H_{14}O_4Na$: 197.0785, found: 197.0784.

7: Amberlyst 15 (24.2 mg, 20 wt %) was added to a solution of diol **6** (118 mg, 0.677 mmol) in THF (9.7 mL), H_2O (0.97 mL), and acetone (0.97 mL), and the reaction mixture was stirred at 80 °C for 15 h. The reaction solution was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 1:3) to afford (*R*)-4-hydroxy-2-cyclohexen-1-one (**7**) (64.6 mg, 0.576 mmol, 85 %) as a dark red oil. $[\alpha]_D^{30} = +92.3$ ($c = 0.7$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 3419$, 2954, 2871, 1660, 1205, 1066, 970, 943, 864 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.94$–2.02 (1H, m), 2.30–2.40 (2H, m), 2.45 (1H, s), 2.56 (1H, dt, $J = 17.4$, 4.7 Hz), 4.56 (1H, ddd, $J = 6.8$, 4.7, 2.2 Hz), 5.94 (1H, d, $J = 10.0$ Hz), 6.92 ppm (1H, dt, $J = 10.0$, 1.8 Hz); ^{13}C NMR ($CDCl_3$): $\delta = 32.4$, 35.3, 66.3, 129.2, 152.9, 198.9 ppm.

(*R*)-*tert*-Butyldimethylsiloxy-2-cyclohexen-1-one: Imidazole (168 mg, 2.47 mmol) was added to a solution of enone **7** (100 mg, 0.892 mmol) and TBSCl (341 mg, 2.27 mmol) in DMF (1.8 mL) at 0 °C, and the reaction mixture was stirred for 1 h. The reaction was quenched with pH 7.0 phosphate buffer, and organic materials were extracted with EtOAc. The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo and purified by silica-gel column chromatography (hexane/EtOAc = 30:1) to afford (*R*)-*tert*-butyldimethylsiloxy-2-cyclohexen-1-one (151 mg, 0.663 mmol, 75 %) as a pearl-yellow oil. $[\alpha]_D^{30} = +97.9$ ($c = 1.2$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 2954$, 2858, 1691, 1471, 1383, 1252, 1103, 860, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.01$ (3H, s), 0.02 (3H, s), 0.81 (9H, s), 1.90–2.00 (1H, m), 2.10–2.20 (1H, m), 2.31 (1H, ddd, $J = 16.7$, 12.7, 4.5 Hz), 2.53 (1H, dt, $J = 16.7$, 4.5 Hz), 4.49 (1H, tt, $J = 6.8$, 2.0 Hz), 5.88 (1H, d, $J = 10.2$ Hz), 6.79 ppm (1H, dt, J = 10.2, 2.0 Hz); ^{13}C NMR ($CDCl_3$): $\delta = -4.8$, −4.7, 18.0, 25.7, 32.9, 35.4, 66.9, 128.6, 153.9, 198.8 ppm.

8: H_2O_2 (0.88 mL, 7.63 mmol) and triton B (69 μL, 0.15 mmol) were added to a solution of (*R*)-*tert*-butyldimethylsiloxy-2-cyclohexen-1-one (345 mg, 1.52 mmol) in THF (9.5 mL) at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine and dried over $NaSO_4$. The organic phase was concentrated in vacuo and purified by silica-gel column chromatography (hexane/EtOAc = 50:1) to afford (2*S*,3*R*,4*R*)-4-*tert*-butyldimethylsiloxy-2,3-epoxycyclohexan-1-one (**8**) (280 mg, 1.16 mmol, 76 %) as a colorless oil. $[\alpha]_D^{30} = -48.5$ ($c = 1.0$, $CHCl_3$); IR (KBr): $\tilde{\nu} = 2954$, 2858, 1716, 1473, 1362, 1254, 1092, 981, 839, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 0.03$ (3H, s), 0.04 (3H, s), 0.81 (9H, s), 1.59–1.66 (1H, m), 1.97–2.05 (1H, m), 2.20–2.35 (2H, m), 3.18 (1H, d, $J = 3.9$ Hz), 3.38 (1H, t, $J = 3.1$ Hz), 4.38 ppm (1H, dd, $J = 6.8$, 3.1 Hz); ^{13}C NMR ($CDCl_3$): $\delta = -5.0$, −4.9, 17.9, 25.4, 25.5, 31.5, 54.8, 57.9, 65.1, 204.7 ppm.

9: *n*-Butyllithium (0.8 mL, 1.55 M in hexane) was added to a stirred solution of HMDS (0.31 mL, 1.5 mmol) in THF (4.1 mL) at 0 °C. After 30 min the reaction mixture was cooled to −78 °C, and a solution of epoxide **8** (100 mg, 0.413 mmol) in THF (1.0 mL) was added. TMSCl (0.26 mL, 2.1 mmol) was then added at −78 °C, and the reaction temperature was increased to −25 °C over 1.5 h. Inorganic materials were removed by filtration through a celite pad, and the filtrate was concentrated in vacuo to give the TMS ether (233.0 mg), which was used directly in the next reaction without purification. $[Pd_2(dba_3)]\cdot CHCl_3$ (60.3 mg, 0.0583 mmol) and diallylcarbonate (56 μL, 0.39 mmol) was added to a solution of the TMS ether in MeCN (6.9 mL), and the mixture was stirred for 4 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the organic materials were extracted with $CHCl_3$ (3×5 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo and was purified by silica-gel column chromatography (hexane/EtOAc = 50:1) to afford (2*S*,3*R*,4*R*)-4-*tert*-butyldimethylsiloxy-2,3-epoxy-5-cyclohexen-1-one (**9**) (77.4 mg, 0.322 mmol, 78 %) as a colorless oil. $[\alpha]_D^{20} =$

−265 (c = 1.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 2956, 2931, 2858, 1693, 1261, 1092, 839, 806, 779 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.12 (3H, s), 0.15 (3H, s), 0.89 (9H, s), 3.42–3.42 (1H, m), 3.60–3.62 (1H, m), 4.62–4.63 (1H, m), 5.96 (1H, dt, J = 10.5, 1.3 Hz), 6.53 ppm (1H, ddd, J = 10.5, 4.5, 2.7 Hz); ^{13}C NMR ($CDCl_3$): δ = −4.7, −4.5, 18.1, 25.6, 53.3, 58.4, 63.6, 126.2, 144.3, 193.2 ppm.

10: A solution of iodine (305 mg, 1.20 mmol) in Et_2O (1.5 mL) and pyridine (1.5 mL) was stirred at 0 °C for 20 min in the dark. Enone **9** (144 mg, 0.600 mmol) was added to the reaction mixture at 0 °C, and the reaction temperature was raised to room temperature over 2 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, and the organic materials were extracted with EtOAc. The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo and purified by silica-gel column chromatography (hexane/EtOAc = 50:1) to afford (2*S*,3*R*,4*R*)-4-*tert*-butyldimethylsiloxy-2,3-epoxy-6-iodo-5-cyclohexen-1-one (**10**) (178 mg, 0.485 mmol, 80%) as a colorless oil. $[\alpha]_D^{22}$ = −105.6 (c = 1.2, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 2954, 2858, 1697, 1257, 1092, 872, 835, 781 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.16 (3H, s), 0.18 (3H, s), 0.92 (9H, s), 3.62–3.63 (1H, m), 3.68–3.69 (1H, m), 4.59–4.60 (1H, m), 7.28 ppm (1H, dd, J = 5.0, 2.4 Hz); ^{13}C NMR ($CDCl_3$): δ = −4.7, −4.5, 18.1, 25.6, 51.7, 58.2, 66.1, 101.9, 152.6, 187.5 ppm; HRMS (FAB): calcd for $C_{12}H_{20}IO_3Si$: 367.0227, found: 367.0249.

12: $[Pd_2(dba_3)]\cdot CHCl_3$ (8.2 mg, 8.2 μmol), $AsPh_3$ (7.8 mg, 0.026 mmol), and toluene (0.2 mL) were stirred for 20 min at room temperature. A solution of iodoenone **10** (30 mg, 0.08 mmol) and vinyl stannane **11** (37.6 mg, 0.1 mmol) in toluene (0.5 mL) were added to the reaction mixture, which was stirred at 110 °C for 5 min in toluene. After cooling, inorganic materials were removed by filtration through a celite pad, the filtrate was concentrated in vacuo, and the residue was purified by silica-gel column chromatography (hexane/EtOAc = 5:1) to afford (2*S*,3*R*,4*R*)-4-*tert*-butyldimethylsiloxy-2,3-epoxy-6-(3-hydroxy-3-methylbutenyl)-5-cyclohexen-1-one (**12**) (19.8 mg, 0.0610 mmol) in 77% yield as a colorless oil. Enone **12** is unstable, therefore it was used immediately in the next reaction. ^1H NMR ($CDCl_3$): δ = 0.13 (3H, s), 0.16 (3H, s), 0.90 (9H, s), 1.33 (3H, s), 1.35 (3H, s), 3.46 (1H, d, J = 3.3 Hz), 3.60–3.65 (1H, m), 4.72 (1H, d, J = 4.9 Hz), 6.28 (1H, d, J = 16.1 Hz), 6.38 (1H, s), 6.41 ppm (1H, d, J = 16.1 Hz).

1: Excess NH_4F (23.7 mg, 0.641 mmol) was added to a solution of **12** (19.8 mg, 0.0610 mmol) in MeOH (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h and then concentrated in vacuo. The residue was purified by thin-layer chromatography (MeOH/$CHCl_3$ 1:10) to afford monomer **2** (9.3 mg, 0.044 mmol) in 75% yield. The monomer **2** was allowed to stand at room temperature for 33 h and purified thin-layer chromatography (MeOH/$CHCl_3$ 1:10) to afford panepophenanthrin (**1**) (9.2 mg, 0.02 mmol, 95%) as a white solid. Monomer (**2**) ^1H NMR ($CDCl_3$): δ = 1.04 (3H, s), 1.05 (3H, s), 3.31 (1H, d, J = 3.5 Hz), 3.53–3.55 (1H, m), 4.50 (1H, d, J = 5.1 Hz), 6.05 (1H, d, J = 16.1 Hz), 6.18 (1H, d, J = 16.1 Hz), 6.32 ppm (1H, dd, J = 5.1, 2.4 Hz). Panepophenanthrin (**1**): $[\alpha]_D^{24}$ = +147.2 (c = 0.91, MeOH); lit. $[\alpha]_D^{26}$ = +149.8 (c = 1.0, MeOH);[1] IR (KBr): $\tilde{\nu}$ = 2978, 1676, 1597, 1338, 1142, 997 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.17 (3H, s), 1.20 (3H, s), 1.35 (3H, s), 1.45 (3H, s), 2.03 (1H, br d, J = 9.7 Hz), 2.32 (1H, br d, J = 10.0 Hz), 3.31 (1H, d, J = 4.0 Hz), 3.35 (1H, dd, J = 5.0, 1.6 Hz), 3.42 (1H, d, J = 4.0 Hz), 3.50 (1H, t, J = 3.2 Hz), 3.84 (1H, t, J = 3.4 Hz), 4.35 (1H, br s), 4.55 (1H, br s), 5.68 (1H, d, J = 16.2 Hz), 5.99 (1H, d, J = 16.2 Hz), 6.81 ppm (1H, dd, J = 5.0, 3.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 26.2, 29.5, 30.3, 32.3, 50.0, 51.2, 55.1, 55.6, 57.1, 57.2, 57.4, 60.7, 66.2, 69.0, 71.8, 79.2, 102.7, 129.3, 138.8, 139.9, 143.0, 196.3 ppm.

16: $[Pd(PhCN)_2Cl_2]$ (7.4 mg, 0.02 mmol) was added to a solution of iodoenone **10** (23.5 mg, 0.0642 mmol), 1-propen-1-ylboronic acid (**13**) (11.0 mg, 0.128 mmol), Ag_2O (23.8 mg, 0.103 mmol), and $AsPh_3$ (11.8 mg, 0.04 mmol) in THF/H_2O (8:1, 1.4 mL), and the reaction mixture was stirred at room temperature for 30 min in the dark. Saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture, which was stirred for 1 h at that temperature. The organic materials were extracted with EtOAc (5 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo and purified by thin-layer chromatography (hexane/EtOAc = 30:1) to afford (2*S*,3*R*,4*R*)-6-butenyl-4-*tert*-butyldimethylsiloxy-2,3-epoxy-5-cyclohexen-1-one (**16**) (16.5 mg, 0.0590 mmol, 92%) as a colorless oil. As **16** was unstable, it was used immediately in the next reaction. ^1H NMR ($CDCl_3$): δ = 0.12 (3H, s), 0.15 (3H, s), 0.90 (9H, s), 1.79 (3H, d, J = 6.4 Hz), 3.42 (1H, d, J = 4.0 Hz), 3.62 (1H, s), 4.71 (1H, d, J = 4.0 Hz), 6.10 (1H, d, J = 16.2 Hz), 6.19–6.26 (1H, m), 6.30–6.40 ppm (1H, m).

19: Excess NH_4F (20.5 mg, 0.554 mmol) was added to a solution of the siloxy monomer **16** (15.5 mg, 0.0553 mmol) in MeOH (3 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h and then concentrated in vacuo. The residue was purified by thin-layer chromatography (MeOH/$CHCl_3$ = 1:1) to afford the monomer. The monomer was allowed to stand at room temperature for 5 h to afford RKTS-80 (**19**) (15.0 mg, 0.05 mmol) in 80% yield as a white solid. $[\alpha]_D^{22}$ = +83.1 (c = 0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3419, 2923, 2854, 1698, 1633, 1455, 1259, 1085 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.87 (3H, d, J = 7.2 Hz), 1.67 (3H, dd, J = 6.5, 1.5 Hz), 2.35–2.38 (1H, m), 2.60–2.70 (1H, m), 2.90–3.00 (1H, m), 3.23 (1H, d, J = 3.4 Hz), 3.29 (1H, d, J = 3.4 Hz), 3.50 (1H, d, J = 3.4 Hz), 3.52 (1H, d, J = 3.4 Hz), 3.91 (1H, d, J = 9.0 Hz), 4.58 (1H, d, J = 4.2 Hz), 5.20–5.40 (1H, m), 5.56 (1H, dd, J = 16.2, 1.5 Hz), 6.60 ppm (1H, dd, J = 4.7, 2.3 Hz); ^{13}C NMR ($CDCl_3$): δ = 15.2, 18.4, 29.6, 34.5, 44.8, 53.3, 53.6, 58.1, 61.9, 66.5, 70.6, 76.4, 129.1, 131.0, 131.8, 142.6, 195.4, 203.0 ppm; HRMS (FAB): calcd for $C_{18}H_{21}O_6$: 333.1338, found: 333.1357.

(2*S*,3*R*,4*R*)-4-*tert*-Butyldimethylsiloxy-2,3-epoxy-6-hexenyl-5-cyclohexen-1-one (**17**), (2*S*,3*R*,4*R*)-4-*tert*-butyldimethylsiloxy-6-decenyl-2,3-epoxy-5-cyclohexen-1-one (**18**), RKTS-81 (**20**), and RKTS-82 (**21**) were prepared by the same procedure as that for RKTS-80 (**19**). The physical data for these compounds are detailed below.

17: ^1H NMR ($CDCl_3$): δ = 0.13 (3H, s), 0.15 (3H, s), 0.90 (9H, s), 1.21–1.40 (9H, m), 3.51 (1H, d, J = 4.4 Hz), 3.62 (1H, s), 4.71 (1H, d, J = 4.4 Hz), 6.08 (1H, d, J = 16.1 Hz), 6.18–6.32 (1H, m), 6.30–6.37 ppm (1H, m).

20: $[\alpha]_D^{21}$ = +25.8 (c = 0.2, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3444, 2927, 2857, 1698, 1635, 1465, 1268 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.80–0.90 (6H, m), 1.20–1.28 (12H, m), 2.47 (1H, dd, J = 6.0, 3.8 Hz), 2.72–2.79 (1H, m), 2.80–2.87 (1H, m), 3.29 (1H, d, J = 3.3 Hz), 3.33 (1H, d, J = 3.3 Hz), 3.53 (1H, d, J = 3.3 Hz), 3.56 (1H, d, J = 3.3 Hz), 4.03 (1H, d, J = 9.2 Hz), 4.75 (1H, d, J = 3.8 Hz), 5.30 (1H, td, J = 16.4, 6.8 Hz), 5.59 (1H, d, J = 16.4 Hz), 6.78 ppm (1H, dd, J = 2.8, 2.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 13.8, 22.2, 22.6, 29.5, 29.7, 30.4, 31.0, 32.6, 39.9, 44.6, 47.0, 53.3, 53.4, 53.9, 57.5, 61.7, 67.4, 71.6, 130.1, 131.6, 134.8, 142.3, 194.5, 202.4 ppm; HRMS (FAB): calcd for $C_{24}H_{33}O_6$: 417.2277, found: 417.2265.

18: ^1H NMR ($CDCl_3$): δ = 0.12 (3H, s), 0.15 (3H, s), 1.00 (9H, s), 1.15–1.30 (17H, m), 3.49 (1H, d, J = 4.1 Hz), 3.62 (1H, s), 4.71 (1H, d, J = 4.1 Hz), 6.08 (1H, d, J = 15.8 Hz), 6.17–6.28 (1H, m), 6.30–6.37 ppm (1H, m).

21: $[\alpha]_D^{23}$ = +33.8 (c = 0.1, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3434, 2925, 2854, 1702, 1465, 1270, 1054 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 0.84–0.87 (6H, m), 1.00–1.06 (28H, m), 2.46 (1H, dd, J = 6.3, 4.0 Hz), 2.72–2.80 (1H, m), 2.80–2.86 (1H, m), 3.28 (1H, d, J = 3.3 Hz), 3.32 (1H, d, J = 3.3 Hz), 3.53 (1H, d, J = 3.3 Hz), 3.55 (1H, d, J = 3.3 Hz), 4.03 (1H, d, J = 9.2 Hz), 4.75 (1H, d, J = 4.0 Hz), 5.30 (1H, td, J = 6.9, 16.3 Hz), 5.58 (1H, d, J = 16.3 Hz), 6.78 ppm (1H, dd, J = 5.0, 2.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 14.1, 22.6, 27.4, 28.9, 29.15, 29.22, 29.3, 29.4, 29.6, 29.7, 30.8, 31.8, 33.0, 40.0, 44.7, 47.1, 53.3, 53.5, 53.9, 57.5, 61.8, 67.5, 71.7, 130.2, 131.6, 134.9, 142.2, 194.5, 202.5 ppm; HRMS (FAB): calcd for $C_{32}H_{49}O_6$: 529.3529, found: 529.3504.

Effect of Solvent and Time on Yield of Diels–Alder Reaction of 2

Three vessels were prepared, in each of which was dissolved monomer **2** (2 mg, 0.01 mmol) in solvent (0.2 mL). The reactions were performed for 5, 22, and 33 h, respectively, at room temperature. Each reaction solution was then concentrated in vacuo, and the NMR spectra were measured in $CDCl_3/CD_3OD$ (10:1). The yield of the dimer was determined by the integral ratio of δ = 6.81 (1H, dd, J = 5.0, 3.0 Hz) and 6.32 ppm (1H, dd, J = 5.1, 2.4 Hz).

Measurement of E1 Activity

The E1 activity was measured on the basis of the formation of the E1–ubiquitin intermediate from E1 and ubiquitin in the presence of ATP. Various concentrations of test compounds were added to 10 μL of the reaction mixture (100 mM tris–HCl pH 9.0, 5 mM $MgCl_2$, 1 mM DTT, 2.5 mM ATP) containing 10 $\mu g\,mL^{-1}$ of E1 enzyme (BostonBiochem, Boston, MA). After incubation for 15 min at room temperature, 100 ng of biotinylated ubiquitin (BostonBiochem) was added to the reaction mixture, and the resulting mixture was incubated further at 37 °C for 15 min. The reaction was terminated by boiling with Laemmli loading buffer. The mixture (10 μL) was loaded on an SDS 7.5% polyacrylamide gel, and electrophoresis was carried out under nonreducing conditions. The proteins were electrically transferred to a PVDF membrane (Millipore, Boston, MA). The membrane was blocked and incubated with streptavidin-conjugated horseradish peroxidase to detect the biotinylated ubiquitin by the enhanced chemiluminescence method (SuperSignal WestPico, Pierce Biotechnology, Rockford, IL). The bands of ubiquitiylated E1 were quantified by Scanning Imager (Molecular Dynamics).

Cell Proliferation Assay in MCF-7 Cells

Human breast cancer MCF-7 cells were grown at 37 °C in a humidified atmosphere containing 5% CO_2 in an RPMI-1640 medium (Sigma, St. Louis, MO) supplemented with 10% fetal calf serum. The cells were seeded at 3×10^3 cells/well in a 96-well plate. After incubating for 18 h at 37 °C, various concentrations of test compounds were added, and further incubated for 48 h at 37 °C. The cell number was evaluated by the subsequent color reaction. WST-8 solution 2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2*H*-tetrazolium monosodium salt (Nakalai tesque, Kyoto) was added to the medium, and the cells were further incubated for 3 h at 37 °C. The absorbance (A_{450}) of each well was measured by using a plate reader (Wallac 1420 multilabel counter) (GE Healthcare Biosciences KK, Tokyo). Cell number (%) was calculated as (experimental absorbance−background absorbance)/(control absorbance−background absorbance)×100.

Acknowledgements

This work was partially supported by a Grand-in-Aid for Scientific Research on Priority Areas (A) "Creation of Biologically Functional Molecules" from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, and also by a grant from the Research Center for Green Photoscience and Technology at the Tokyo University of Science.

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Received: June 26, 2006
Revised: August 4, 2006
Published online: November 14, 2006

