Discovery of an 8-Aza-5-thiaProstaglandin E_1 Analog as a Highly Selective EP4 Receptor Agonist

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For the purpose of discovering an orally available EP4 subtype-selective agonist, a series of 8-aza prostaglandin E_1 (PGE_1) analogs were synthesized and evaluated for their affinity for PGE_2 receptor subtypes. Additionally, the structure–activity relationships of these compounds were studied. Among the tested compounds, the 8-aza PGE_1 analog 6 and 8-aza-5-thiaPGE_1 analog 12 had highly potent EP4 receptor affinity, good functional activity, and excellent subtype-selectivity. Furthermore, these analogs demonstrated good stability in human liver microsomes. As a result, we concluded that these two series of 8-aza PGE_1 analogs could be promising chemical leads for an orally available EP4 subtype-selective agonist.

Key word prostaglandin; agonist; EP4 receptor

Prostaglandin E_2 (PGE_2) is one of the oxidative metabolites of arachidonic acid produced by cyclooxygenase, and is involved in a number of significant physiological processes. Receptors for PGE_2 (EPs) are classified into four subtypes: EP1, EP2, EP3 and EP4. Each subtype mediates different effects in various tissues and cells.[1] The EP4 receptor is found to be distributed in the thymus, lungs, heart, kidneys, bone, uterus and other organs, and mediates the production of intracellular cyclic adenosine monophosphate (cAMP). Various biological actions of PGE_2, such as its cytoprotective action, improvement of blood flow, regulation of inflammatory cytokine production and bone resorption/formation, are thought to be mediated *via* the EP4 subtype.[2—4] Accordingly, a highly potent EP4 selective agonist is expected to have potential therapeutic effects on rheumatoid arthritis and other diseases without the adverse effects that occur with other EP subtypes.

We previously reported on the discovery of 3,7-dithia-16-phenyl-PGE_1 **1** (Fig. 1), which is often used as a probe, specifically a highly selective EP4 agonist, in investigating the role of EP4 receptors.[5] 5-ThiaPGE_1 **2** was also found to be an optimized structure that functions as a highly selective EP4 receptor agonist (Fig. 1). As a result, the 3,7-dithia and 5-thia moieties were considered to be structural requirements of EP4 subtype-selectivity. However, the chemical instability, primarily due to their easily enolizable α-alkylthiocyclopentanone and/or β-hydroxy cyclopentanone, which is susceptible to dehydration, is a major drawback for compounds **1** and **2** in regards to their drug candidacy. Thus, the chemical instability of compounds **1** and **2** needs to be modified so as to identify a drug candidate.

According to our previous report,[5] 3,7-dithia-16-(3-methoxymethylphenyl)methylPGE_1 **1** was found to be an excellent EP4 selective agonist that had an improved EP3/EP4 selectivity (K_i: EP3/EP4=124). Additionally, 5-thia-16-(3-methoxymethylphenyl)methylPGE_1 **2** was also found to have potent affinity for the EP4 subtype and a good EP3/EP4 selectivity (K_i: EP3/EP4=80),[6] however it had potent binding affinity for both the EP3 and EP4 subtypes. Based on this observation, the 3,7-dithia moiety of **1** and the 5-thia moiety of **2** were hypothesized to play an important role in the subtype selectivity of EP3 and EP4. In the molecular design process, we first focused on the easily enolizable α-alkylthiocyclopentanone moiety of 3,7-dithiaPGE_1 **1**, since compound **1** had an equilibrium mixture with its 8-epimer **1′** (**1**/**1′**=7/3), as determined with ^{1}H-NMR. Based on the analysis described above, the 3,7-dithiaPGE_1 analog **1** was predicted to occupy a planar enol form during the epimerization process (Fig. 2). Specifically, the sulfur atom at position-7 may occupy the same plane, which consists of three carbon atoms (C-8, C-9, C-10) of the cyclopentanone ring. To confirm our hypothesis, 7,8-unsaturated PGE_1 analog **3** and 8,9-unsaturated cyclopentene PG analog **4** (Fig. 3), with four carbon atoms (C-7, C-8, C-9, C-10) occupying a single plane, were synthesized and biologically evaluated.

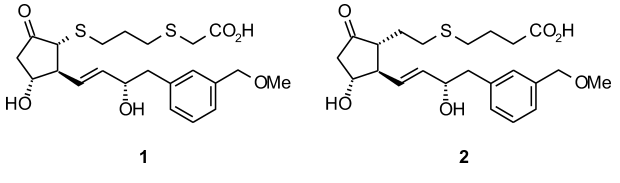

Fig. 1. Reported Structures of Potent and Selective EP4 Agonists

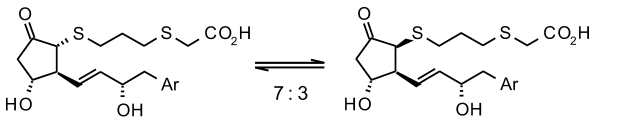

Fig. 2. An Easily Enolizable Structure

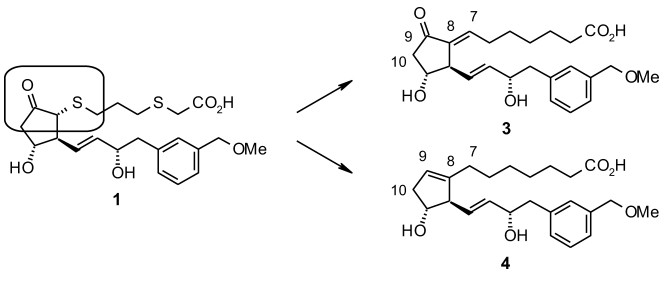

Fig. 3. Structural Mimetics **3** and **4** of the Enol Form of **1**

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Herein, we report the discovery of 8-aza-16-phenyl-PGE_1 analogs that are more chemically stable than compounds **1** and **2**, as well as function as highly selective EP4 agonists.

Chemistry Analogs **3** and **4** were synthesized as described in Charts 1 and 2, respectively. A Michael addition reaction of the vinyl iodide **20**[7] with a commercially available enone **16**, and the trapping of the resulting enolate anion with an aldehyde **21** yielded **17**.[8] Compound **17** was then converted into analog **3** by the following sequential reactions: (1) mesylation of the hydroxyl group followed by the elimination with a methanesulfonyl chloride and 4-dimethylaminopyridine (DMAP), (2) deprotection with $(HF)_n$-py, and (3) enzymatic hydrolysis with porcine liver esterase (PLE).

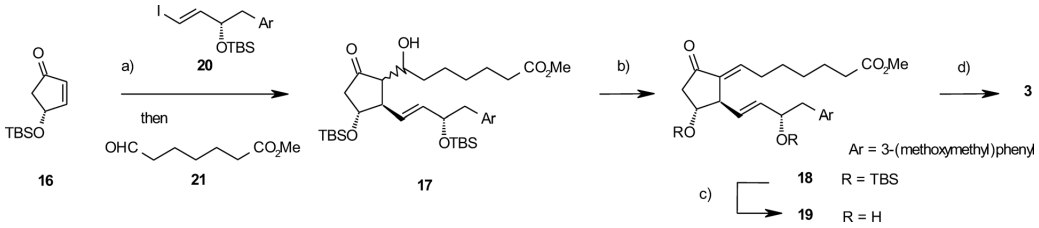
Furthermore, as shown in Chart 2, the Michael addition reaction of the vinyl iodide **20** with a commercially available enone **22**, followed by the trapping of the resulting enolate anion with *N*,*N*-trifluoromethanesulfonylaniline, yielded an enol triflate **23**. Palladium-catalyzed removal of the trifluoromethanesulfonyloxy moiety from compound **23**, followed by the deprotection with $(HF)_n$-py, and then the enzymatic hydrolysis with PLE, resulted in analog **4**.

The synthesis of 11-deoxy analog **5** was described in Chart 3. Acidic dehydration of **24** in acetic acid followed by reduction with lithium aluminum hydride in the presence of copper iodide produced **25**. Enzymatic hydrolysis of **25** gave **5**.

The synthesis of analogs **6** and **7** is outlined in Chart 4. *tert*-Butyldimethylsilyl ether (*R*)-**26** and (*S*)-**26** were prepared from commercially available (*R*)/(*S*)-5-(hydroxymethyl)-2-pyrrolidinone, respectively, as previously described.[9] *N*-Alkylation of (*R*)-**26** with ethyl 7-bromohetanoate using sodium hydride in *N*,*N*-dimethylformamide (DMF) produced (*R*)-**27**. Then, the deprotection of TBS with tetrabutylammonium fluoride (TBAF) produced (*R*)-**28**. (*R*)-**28** was then oxidized with a SO_3-Py complex and dimethylsulfoxide in the presence of diisopropylethylamine. Then, following a Horner-Emmons olefination and a reaction with 3-[(3-methoxymethyl)phenyl]-2-oxopropane phosphonate **31** resulted in an (12*R*)-enone **29**. A borane reduction of the enone, which was catalyzed by (*R*)-methyl-Corey–Bakshi–Shibata (CBS)-oxazaborolidine, stereoselectively created an (15*S*)-isomer **30**.[10] Alkaline hydrolysis of the ethyl ester **30** resulted in the production of carboxylic acid **6**. Subsequently, analog **7** was synthesized from the (*S*)-**26**, based on the same procedure used to prepare analog **6** from (*R*)-**26**.

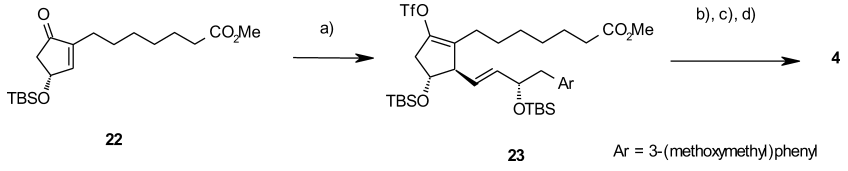
Analogs **8** and **9** were prepared, as shown in Chart 5. *N*-Acylation of D-prolinol **32** with ethyl 6-(chloroformyl)hexanoate in aqueous sodium hydroxide and dioxane produced **33**. Compound **33** was the converted to **8** using the sequential reactions described above. *O*-Protection of 2-*N*-acetyl aminoethanol **34** was achieved by using a tetrahydropyranyl ether. The product was then *N*-alkylated with an ethyl 7-bromoheptanoate in the presence of sodium hydride, which resulted in the production of **36**. Deprotection of **36** under acidic conditions produced alcohol **37**, which was then transformed into analog **9**, as described in Chart 4.

The synthesis of a sulfonamide analog **10** is outlined in Chart 6. A palladium-catalyzed carbon monoxide insertion into a vinyl iodide **38**, in the presence of methanol, yielded a methyl ester **39**. The methyl ester **39** was then reduced with diisobutylaluminum hydride (DIBAL), and resulted in the



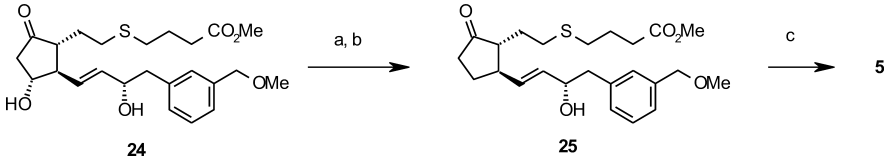
Reagents: a) **20**, *t*-BuLi, lithium (2-thienyl)cyanocuprate, Et_2O, THF then **21**, 25%; b) MsCl, DMAP, CH_2Cl_2, 67%; c) $(HF)_n$-Py, pyridine, CH_3CN, 88%; d) PLE, EtOH, phosphate buffer, 53%.

Chart 1. Synthesis of 7,8-Unsaturated PGE_1 Analog **3**



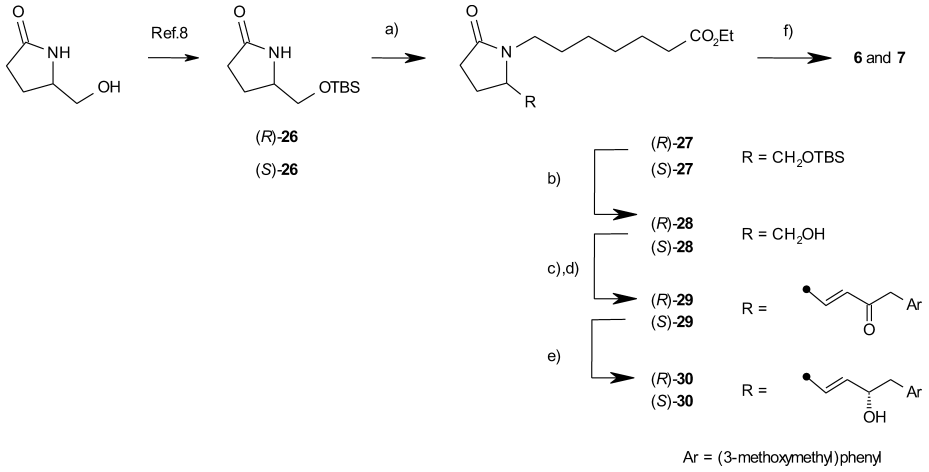
Reagents: a) **20**, *t*-BuLi, lithium (2-thienyl)cyanocuprate, Et_2O, THF then $PhN(Tf)_2$; b) HCO_2H, $Pd(OAc)_2$, PPh_3, Et_3N, DMF; c) $(HF)_n$-Py, pyridine, CH_3CN, 35% from **22**; d) PLE, EtOH, phosphate buffer, 76%.

Chart 2. Synthesis of Cyclopentene PG Analog **4**



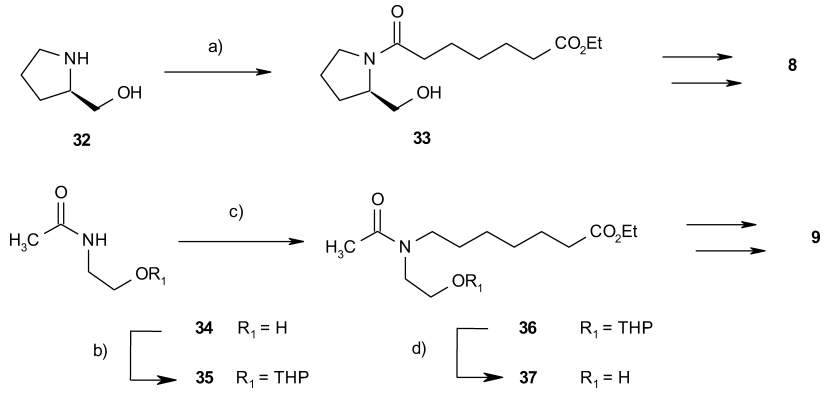
Reagents: a) aq. HCl, AcOH; b) $LiAlH_4$, CuI, HMPA, THF, 74%; c) PLE, EtOH, phosphate buffer, 84%.

Chart 3. Synthesis of 11-Deoxy PG Analog **5**



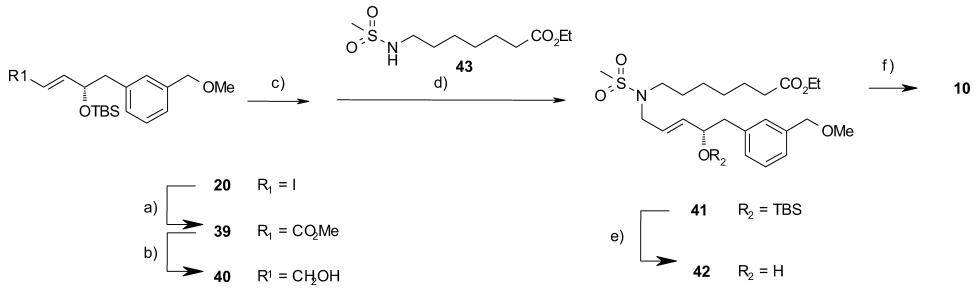
Reagents: a) ethyl 7-bromoheptanoate, NaH, DMF, 63%; b) TBAF, THF, 91%; c) SO_3-Py, DMSO, *i*-Pr_2NEt, DMSO, EtOAc; d) dimethyl 3-[(3-methoxymethyl)phenyl]-2-oxopropanephosphonate **31**, NaH, THF; e) (*R*)-Me-CBS, BH_3-THF, THF; f) aq. NaOH, THF, EtOH.

Chart 4. Synthesis of **6** and **7**



Reagents: a) ethyl 6-(chloroformyl)hexanoate, dioxane, aq. NaOH, 46%; b) 3,4-dihydro-2*H*-pyran, *p*-TsOH, CH_2Cl_2; c) ethyl 7-bromoheptanoate, NaH, DMF; d) *p*-TsOH, EtOH, 50% in 3 steps.

Chart 5. Synthesis of PG Analogs **8** and **9**

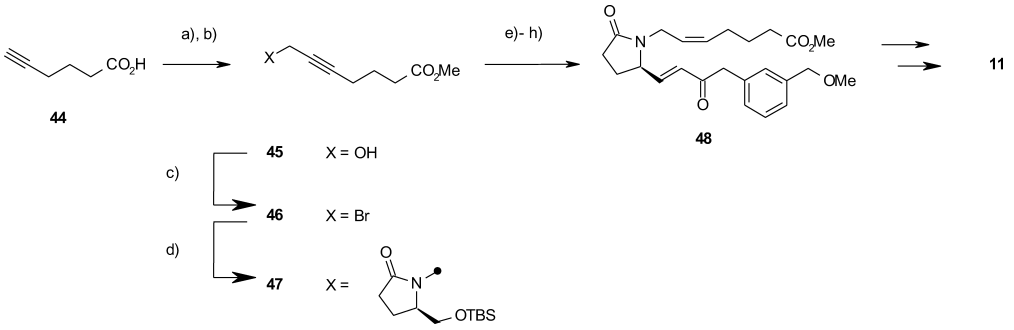


Reagents: a) $(Ph_3P)_2PdCl_2$, CO, Et_3N, MeOH, MeCN, 91%; b) DIBAL, CH_2Cl_2; c) MsCl, Et_3N, THF; d) **43**, NaH, DMF; e) TBAF, THF, 84% in 4 steps; f) aq. NaOH, MeOH, 99%.

Chart 6. Synthesis of Sulfonamide Analog **10**

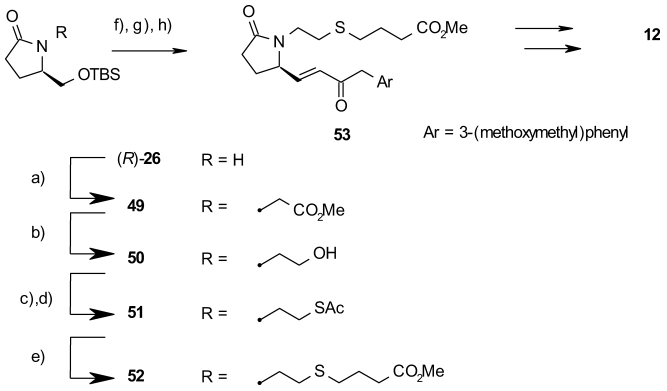
production of an allyl alcohol **40**. Methanesulfonylation of **40** yielded a methanesulfonate, which was then used in the *N*-alkylation of a sulfonamide **43**, in the presence of sodium hydride, resulting in **41**.[11,12] Deprotection of TBS with tetrabutylammonium fluoride (TBAF), followed by alkaline hydrolysis, produced analog **10**.

An 8-aza-PGE_2 analog **11** was synthesized, as illustrated in Chart 7. First, a dimagnesium salt of **44** was prepared from hex-5-inoic acid and ethylmagnesium bromide. The dimagnesium salt of **44** underwent an addition reaction with paraformaldehyde, which was then followed by esterification with trimethylsilyldiazomethane, and produced compound **45**. Bromination of **45** with carbon tetrabromide and triphenylphosphine yielded a bromide **46**. *N*-Alkylation of (*R*)-**26** with the bromide **46** in the presence of sodium hydride produced **47**, which was then transformed into **48** by the following sequential reactions: (1) catalytic partial hydrogenation with a Lindlar catalyst in the presence of cyclohexene,



Reagents: a) EtMgBr, $(HCHO)_n$, THF; b) $TMSCHN_2$, MeOH, 60%; c) CBr_4, PPh_3, CH_2Cl_2, 69%; d) (*R*)-**26**, NaH, DMF, 78%; e) H_2, Lindlar catalyst, cyclohexene, benzene; f) *p*-TsOH, MeOH; g) SO_3-Py, Et_3N, DMSO, CH_2Cl_2; h) NaH, phosphonate **31**, THF, 66% in 4 steps.

Chart 7. Synthesis of 8-Aza-PGE_2 Analog **11**



Reagents: a) methyl bromoacetate, NaH, DMF, 61%; b) $NaBH_4$, MeOH; c) MsCl, *i*-Pr_2NEt, THF; d) KSAc, DMF, 71% in 3 steps; e) methyl 4-iodobutyrate, K_2CO_3, MeOH, 94%; f) TBAF, THF; g) SO_3-Py, Et_3N, DMSO, CH_2Cl_2; h) NaH, phosphonate **31**, THF, 48% in 3 steps.

Chart 8. Synthesis of 8-Aza-5-thiaPGE_1 **12**

(2) acidic deprotection of TBS with *p*-toluenesulfonic acid in methanol, (3) oxidation with a SO_3-Py complex and dimethylsulfoxide in the presence of triethylamine, and (4) Horner-Emmons olefination. Compound **48** was then converted into analog **11**, as described above with the preparation of **6**, **7** from **29** (Chart 4).

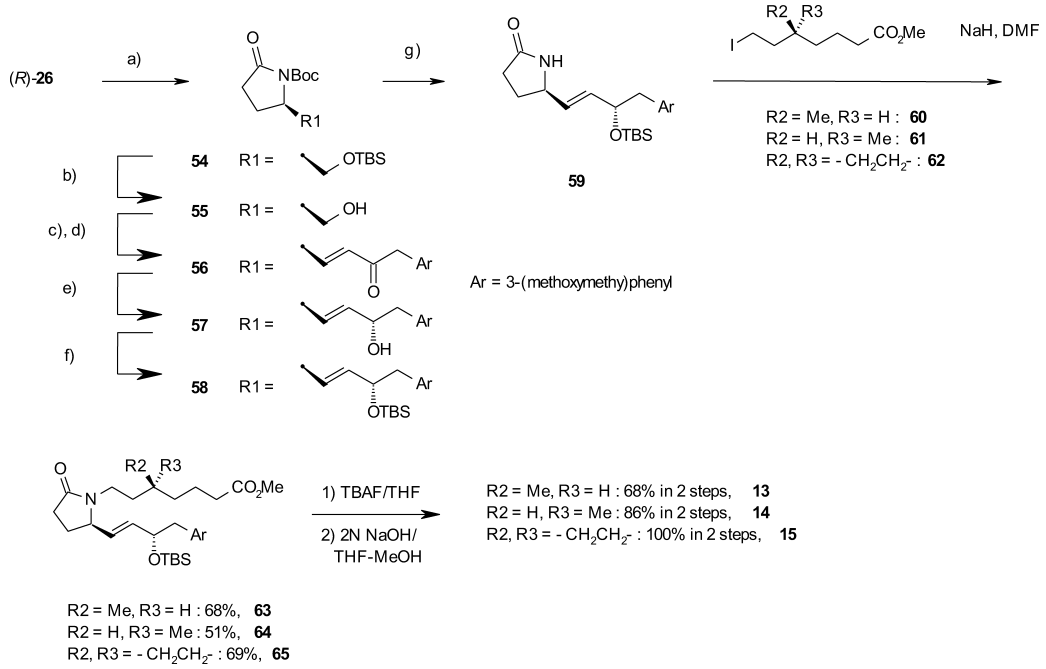
The synthesis of an 8-aza-5-thiaPGE_1 analog **12** is outlined in Chart 8. *N*-Alkylation of (*R*)-**26** with methyl bromoacetate produced compound **49**. A sodium borohydride reduction of compound **49** yielded compound **50**. Methanesulfonylation of compound **50**, followed by a substitution reaction with potassium thioacetate, produced compound **51**. Deacetylation, followed by *S*-alkylation of compound **51**, was achieved with potassium carbonate in methanol and in the presence of methyl 4-iodobutyrate, which produced compound **52**. After deprotection with TBAF, compound **52** was transformed into compound **53** *via* oxidation followed by a Horner–Emmons olefination. Compound **53** was then converted into analog **12** using the conventional procedure for the ω-chain synthesis of PGs.

The synthesis of analogs **13**, **14**, and **15** is presented in Chart 9. *N*-Protection of (*R*)-**26** with Boc_2O yielded compound **54**. Deprotection of compound **54** with tetrabutylammonium fluoride (TBAF) resulted in compound **55**. Oxidation of compound **55** with a SO_3-pyridine complex and dimethylsulfoxide in the presence of triethylamine, followed by the conventional Horner–Emmons olefination, produced compound **56**. Stereoselective reduction of the enone **56** with borane and (*R*)-methyl-CBS-oxazaborolidine yielded an (15*S*)-alcohol **57**. Protection of the resulting 15-hydroxy group on compound **57** with a TBS ether produced compound **58**, whereas deprotection of compound **58** with magnesium methoxide in methanol yielded compound **59**. *N*-Alkylation of compound **59** with alkyl iodides **60**—**62** produced compounds **63**—**65** in the presence of sodium hydride. Deprotection of compounds **63**—**65** with TBAF, followed by alkaline hydrolysis, produced analogs **13**, **14**, and **15**, respectively.

The preparation of methyl 7-iodo-(5*S*)-methylheptanoate **60**, which was used in the synthesis of compound **63**, is described in Chart 10. *O*-Protection of (−)-β-citronellol with a TBS ether, followed by ozonolysis, resulted in an aldehyde **66**. A sodium borohydride reduction of compound **66** produced an alcohol **67**. *p*-Toluenesulfonylation of compound **67** with *p*-toluenesulfonyl chloride in pyridine, followed by a substitution reaction with sodium cyanide in dimethyl sulfoxide (DMSO), resulted in a nitrile **68**. The nitrile **68** was then converted into a hydroxyl ester **70** in three steps. Methanesulfonylation of **70**, followed by nucleophilic substitution with sodium iodide, produced an iodide **60**.

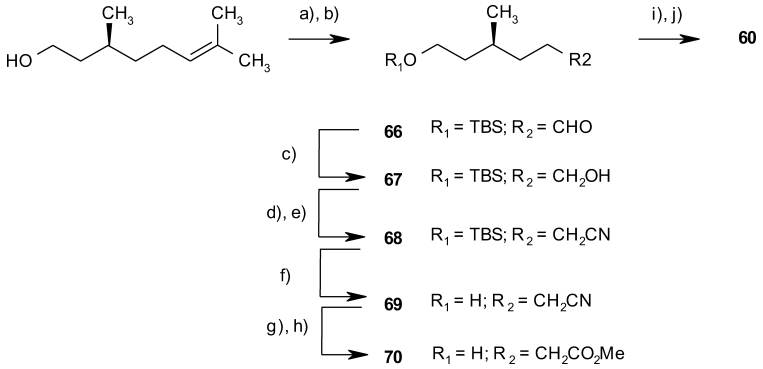
The preparation of methyl 7-iodo-(5*R*)-methylheptanoate **61** is outlined in Chart 11. Compound **67**, which was used as a common intermediate to prepare both enantiomers **60** and **61**, was transformed into **71** by the following sequential reactions: a) oxidation with SO_3-Py and triethylamine in dimethylsulfoxide, b) an addition of methylmagnesium bromide, and c) another oxidation reaction. *C*-2 homologation of compound **71**, which produces compound **72**, was achieved *via* the following sequential reactions: d) deprotection with TBAF, e) oxidation with pyridinium chlorochromate (PCC), f) a Horner–Emmons olefination with methyl diethylphosphonoacetate in the presence of sodium hydride, and g) a catalytic hydrogenation. A Baeyer–Villiger oxidation of compound **72** with *m*-chloroperbenzoic acid (*m*-CPBA) yielded compound **73**, which was converted into compound **61** *via* the following three step reaction: i) methanolysis with methanol in the presence of potassium carbonate, j) methanesulfonylation *via* the conventional method, and k) a substitution reaction with sodium iodide in acetone.

Methyl 5,5-dimethylene-7-iodo-heptanoate **62** was prepared, as illustrated in Chart 12. *O*-Acetylation of homo-



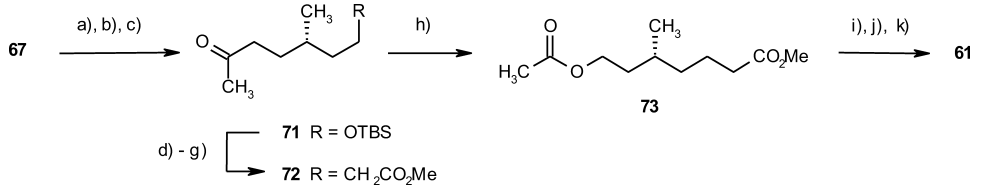
Reagents: a) Boc_2O, DMAP, THF; b) TBAF, THF, 75% in 2 steps; c) SO_3-Py, *i*-Pr_2NEt, DMSO, AcOEt; d) phosphonate **31**, NaH, THF, 65% in 2 steps; e) (*R*)-Me-CBS, BH_3-THF, THF, 85%; f) TBSCl, imidazole, DMF; g) $Mg(OMe)_2$, MeOH; 71% in 2 steps.

Chart 9. Synthesis of 8-Aza-PGE_1 Analogs **13**, **14**, and **15**



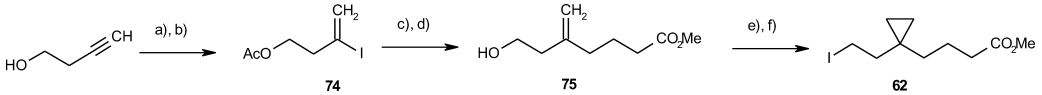
Reagents: a) TBSCl, imidazole, DMF; b) O_3, Me_2S, MeOH, CH_2Cl_2, 70%; c) $NaBH_4$, MeOH, 72%; d) TsCl, pyridine; e) NaCN, DMSO, 93%; f) TBAF, THF, 77%; g) KOH, EtOH, H_2O; h) CH_2N_2, Et_2O, 91%; i) MsCl, Et_3N, CH_2Cl_2; j) NaI, acetone; 67%.

Chart 10. Preparation of Methyl 7-Iodo-(5*S*)-methylheptanoate **60**



Reagents: a) SO_3-Py, Et_3N, DMSO, EtOAc; b) MeMgBr, THF; c) SO_3-Py, Et_3N, DMSO, EtOAc, 62%; d) TBAF, THF, 83%; e) PCC, CH_2Cl_2; f) $MeO_2CCH_2PO(OEt)_2$, NaH, THF, 82%; g) H_2, Pd/C, MeOH, 95%; h) *m*-CPBA, CH_2Cl_2; i) K_2CO_3, MeOH, 65%; j) MsCl, Et_3N, CH_2Cl_2; k) NaI, acetone, 65%.

Chart 11. Preparation of 7-Iodo-(5*R*)-methylheptanoate **61**



Reagents: a) Ac_2O, pyridine; b) NaI, TMSCl, MeCN, H_2O, 47%; c) $IZn(CH_2)_3CO_2Me$, $Pd(PPh_3)_4$, DMF, 68%; d) K_2CO_3, MeOH, 90%; e) Et_2Zn, CH_2I_2, CH_2Cl_2, 36%; f) I_2, Ph_3P, imidazole, DMF, 81%.

Chart 12. Preparation of Methyl 5,5-Dimethylene-7-iodoheptanoate **62**

propargyl alcohol, followed by iodination with sodium iodide, produced a vinyl iodide **74**.[13] A cross-coupling reaction with compound **74** and 3-methoxycarbonylpropyl zinc iodide in the presence of tetrakis(triphenylphosphine)palladium, followed by deacetylation, yielded compound **75**. Lastly, a cyclopropanation reaction with compound **75** under Simmons–Smith conditions, followed by a substitution reaction with iodine in the presence of triphenylphosphine, resulted in an iodide **62**.

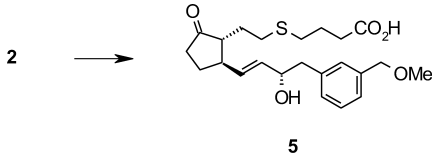
Results and Discussion

The compounds listed in Tables 1—3 were evaluated for their binding affinity for mouse EP receptor subtypes. The agonist activities of these compounds on each of the EP4 receptor subtype were also evaluated (Table 3).

As shown in Table 1, analog **3** demonstrated excellent EP4 selectivity, while its potency was significantly decreased. The structure–activity relationship (SAR) also demonstrated that the cyclopentene analog **4** had improved EP3/EP4 selectivity compared with compound **2**. On the other hand, compound **5**, which is 11-deoxy derivative of **2**, showed quite good EP3/EP4 selectivity maintaining good EP4 receptor affinity (Fig. 4). Thus, the 11-hydroxy residue, which is one of the reasons for chemical instability, was suggested to be removable without reduction of EP4 subtype-selectivity.

Table 1. Binding Affinity of Analogs **1**—**5** for Each of EP Receptor Subtypes

Compound	Binding affinity K_i (nM)			
	mEP1	mEP2	mEP3	mEP4
1	$>10^4$	2100	1200	9.7
2	$>10^4$	620	56	0.7
3	$>10^4$	$>10^4$	$>10^4$	80
4	$>10^4$	1600	$>10^4$	79
5	$>10^4$	470	190	2.4



5

Fig. 4. 11-Deoxy Analog **5**

Based on these observations, we synthesized and evaluated 8-aza-lactam analogs, such as **6** (Table 2), which had four atoms (*i.e.* C-7, N-8, C-9, C-10) corresponding with the C-7, C-8, C-9 and C-10 of analog **3** that occupied a single planar conformation, as a result of the double bond character of the amide C–N bond.

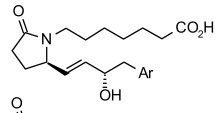
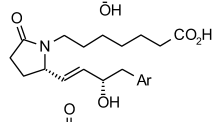
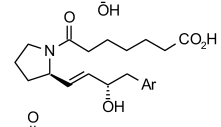
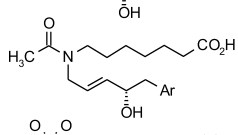
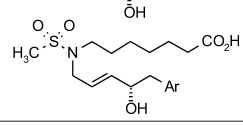
The lactam analog **6**, which has been previously evaluated,[14—17] exhibits potent binding affinity, agonist activity (compound **6** mEP4 $EC_{50}=24$ nM), and excellent EP4 subtype selectivity. Its corresponding 12-*S* isomer **7** was found to be 160-fold less potent in its binding affinity for EP4 receptor, however it still demonstrated subtype selectivity. Thus, the 12*R*-configuration of analog **6** is necessary for its potent binding affinity to EP4 receptor.

The *N*-acyl pyrrolidine analog **8** had a 53-fold lower EP4 binding affinity relative to analog **6** because of the presumed steric and/or electronic factors of the 7-carbonyl moiety of **8** although the planarity of the amide moiety still remains. The *sec*-analog **9** also demonstrated weak affinity for the EP4 receptor, while the corresponding sulfonamide analog **10** did not demonstrate EP4 affinity (*i.e.* up until a concentration of 10^4 nM) possibly due to the non-planarity of its sulfonamide moiety.[11,12] These findings are consistent with the abovementioned SAR.

The α-chain of analog **6** was further optimized so as to improve the activity profiles (Table 3). The introduction of a 5,6-*cis*-double bond into the 8-aza-PGE_1 analog **6** yielded an 8-aza-PGE_2 analog **11**, which had a 4-fold lower EP4 binding affinity and a 20-fold lower agonist activity.

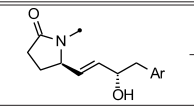
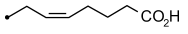
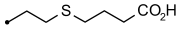
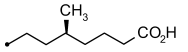
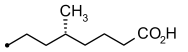
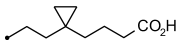
Based on the abovementioned activity profiles of 5-thiaPGE_1 **2**, 8-aza-5-thiaPGE_1 **12** was designed and synthe-

Table 2. Activity Profiles of Various PGE_1 Frameworks Possessing an Optimized ω-Chain

Compound	Structure	Binding affinity K_i (nM)			
		mEP1	mEP2	mEP3	mEP4
6		$>10^4$	$>10^4$	$>10^4$	10
7		$>10^4$	$>10^4$	$>10^4$	1600
8		$>10^4$	$>10^4$	$>10^4$	530
9		$>10^4$	$>10^4$	$>10^4$	250
10		$>10^4$	$>10^4$	$>10^4$	$>10^4$

Ar=3-(Methoxymethyl)phenyl.

Table 3. Activity Profiles of Various α-Chain PG Analogs Possessing an Optimized ω-Chain

Compound		Binding affinity K_i (nM)				EC_{50} (nM)
		mEP1	mEP2	mEP3	mEP4	mEP4
11		$>10^4$	8400	$>10^4$	43	480
12		$>10^4$	8500	$>10^4$	8.0	24
13		$>10^4$	$>10^4$	$>10^4$	28	990
14		$>10^4$	4900	$>10^4$	23	250
15		$>10^4$	2900	$>10^4$	13	710

Ar=3-(Methoxymethyl)phenyl.

sized. Analog **12** was found to have an excellent EP4 selectivity with good agonist activity.[18] Thus, the C-5 of analog **6** may be replaced by a sulfur atom without reducing EP4 affinity, agonist activity and subtype selectivity. Furthermore, analogs **13**—**15** were synthesized and evaluated to investigate the detailed SAR of the C-5-substitutions, specifically the 5*S*-methyl, 5*R*-methyl and 5,5-dimethylene residues. An introduction of the 5-*S* methyl and 5-*R* methyl groups into compound **6** yielded compounds **13** and **14**. Compounds **13** and **14** retained their EP4 selectivity and EP4 receptor affinity; however, they had a 41-fold and 10-fold lower agonist activity, respectively. An introduction of a 5,5-dimethylene residue into compound **6** produced compound **15**, which also retained its EP4 selectivity, but had a 30-fold lower agonist activity. Thus, compounds **11** and **13**—**15** demonstrated an unexpected weak agonist activity for their relatively potent EP4 binding affinity. Both compounds **11** and **14** also demonstrated a 10-fold reduction in their agonist activity. However, the reduction in agonist activity was especially remarkable in analogs **13** (35-fold) and **15** (55-fold). Remarkable reduction of the agonist activity for their potent receptor affinity was considered to be due to their increased protein binding and/or steric factors based on the newly introduced lipophilic alkyl moieties.

Since our purpose has been discovery of an orally available EP4 subtype-selective agonist, representative compounds were evaluated for their metabolic stability in the human liver microsomes. Their agonist activity in rat Chinese hamster ovary (CHO) overexpressing EP4-receptor was also evaluated for the scheduled *in vivo* evaluation in rats. Results are summarized in Table 4.

Compounds **2** and **5** exhibited potent agonist activity while they showed relatively unstable in the human liver microsomes. Compound **6** showed less potent agonist activity relative to **2** and **5** although it showed more stability. The corresponding 5-thia analog **12** exhibited equipotent agonist activity and better stability in the liver microsomes. The 5-thiaPGE_1 analog **2** decomposed due to the oxidation of it sulfur atom at 5-position, while the 8-aza-5-thiaPGE_1 analog **12** was highly stable in liver microsomes despite its 5-thia moiety. The relatively more polar γ-lactam moiety may play a role in preventing the oxidation of compound **12** *via* metabolic enzymes. Thus, replacement of the 5-carbon atom with a sulfur atom was reconfirmed to be effective for the increase of the EP4 affinity and agonist activity while analogous results were reported in our previous report.[7] As a result, 8-aza-5-thiaPGE_1 **12** was considered to be a promising chemical lead for orally active EP4 agonist because of its potent agonist activity with excellent subtype-selectivity.

Table 4. Metabolic Stability in the Human Liver Microsomes and EP4 Agonist Activity in Rat of Representative Compounds

Compound	Functional assay in rat EC_{50} (nM)	Stability in liver microsomes % remaining in HLM[a]
2	1.4	25
5	1.1	4
6	15	72
12	1.3	94

a) HLM: human liver microsomes. Concentration of test compounds, 1 μM; liver microsomes, 1 mg/ml.

In summary, a series of 8-aza-16-phenyl-PGE_1 analogs, which had a γ-lactam moiety instead of the cyclopentanone moiety of PGEs, were found to have potent EP4 agonist activity with good subtype selectivity. Of the compounds tested, analogs **6** and **12** were found to be chemically and metabolically stable EP4 subtype-selective agonists, which demonstrated highly potent EP4 agonist activity with good subtype-selectivity. Furthermore, the g-lactam moiety was found to be a bioisostere of α-alkylthiocyclopentanone moiety of 7-thiaPGE analogs. Further research optimizing these compounds so as to produce orally available EP4 agonists is warranted.

Experimental

mEP1-4 Receptor Binding Assay Competitive binding studies were conducted using radiolabeled ligands and membrane fractions prepared from CHO cells, which stably express the prostanoid receptors mEP1—4. Membranes from CHO cells expressing prostanoid receptors were incubated with a radiolabeled ligand (*i.e.* 2.5 nM [^{3}H]PGE_2) and test compounds at various concentrations in an assay buffer (*i.e.* 10 mM KH_2PO_4–KOH buffer containing 1 mM ethylenediaminetetraacetic acid (EDTA), 10 mM $MgCl_2$ and 0.1 mM NaCl, pH 6.0). Incubation was carried out at 25 °C for 60 min, with the exception of mEP1, which was incubated for 20 min. Incubation was terminated *via* filtration through a Whatman GF/B filter. The filter was subsequently washed with ice-cold buffer (10 mM KH_2PO_4–KOH buffer containing 0.1 mM NaCl, pH 6.0), and the radioactivity on the filter was measured in a 6 ml liquid scintillation (ACSII) mixture with a liquid scintillation counter. Non-specific binding was achieved by adding excess amounts of unlabeled PGE_2 in the assay buffer. The concentration that causes 50% of inhibition (IC_{50} value) was estimated from the regression curve. The K_i value (*M*) was calculated according to the following equation: $K_i = IC_{50}/(1 + [L]/K_d)$, where $[L]$ is the concentration of radiolabeled ligand and K_d is the dissociation constant of radiolabeled ligand for the prostanoid receptor of interest.

Measurement of cAMP Production CHO cells expressing mouse/rat

EP4-receptor were cultured in 24-well plates (1×10^5 cells/well). After 2 d, the media were removed and cells were washed with 500 μl of minimum essential medium (MEM) and incubated for 10 min in 500 μl of buffer (MEM containing 2 μM of diclofenac) at 37 °C. After the removal of buffer *via* suction, cells were pre-incubated in 450 μl of assay medium (containing 1% of bovine serum albumin (BSA)) for 10 min at 37 °C. The reaction was started with the addition of each test compound in 50 μl of assay buffer. After incubation for 10 min at 37 °C, the reaction was terminated by adding 500 μl of ice-cold 10% trichloroacetic acid. cAMP production was determined *via* a cAMP radioimmunoassay kit (Amersham).

Human Microsome Stability Assessments The test compound (5 μl, 10 mm in DMSO) was diluted in 995 μl of 50% acetonitrile in water to make a 50 μM solution. Phosphate buffer (0.1 M, 245 μl) containing 1 mg/ml human liver microsomes and reduced nicotinamide adenine dinucleotide phosphate (NADPH)-*co*-factor was added into a reaction container, prewarmed to 37 °C in a water bath, and incubated for 5 min. The reaction was initiated by the addition of 5 μl of the solution containing the test compound (in 0.975% acetonitrile with 0.05% DMSO, final concentration of 1 μM). Immediately after the initiation of the reaction, a 20 μl aliquot was taken from the solution and transferred into 180 μl of acetonitrile containing the internal standard (candesartan) to terminate the reaction. A 20 μl aliquot of the mixture was mixed with 180 μl of 50% acetonitrile on a plate with a filter for deproteinization and filtered by suction. The filtrate was used as a standard sample. After incubation for 60 min, a 20 μl aliquot was taken from the solution and then underwent the abovementioned procedure to obtain a reaction sample. The obtained samples were measured on an LC-MS/MS system. The percent remaining (%) was calculated by dividing the peak area ratio (*i.e.*, test compound/I.S.) for the reaction sample by the peak area ratio for the standard sample and multiplying by 100.

General Procedure Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were taken on a Varian Mercury 300 spectrometer, Varian GEMINI-200 or VXR-200s spectrometer using deuterated chloroform ($CDCl_3$) as the solvent. Fast atom bombardment (FAB-MS, high resolution (HR)-MS) and electron ionization (EI) mass spectra were obtained on a JEOL JMS-DX303HF spectrometer. Atmospheric pressure chemical ionization (APCI) mass spectra were determined on a HITACHI MI200H spectrometer. Infrared spectra (IR) were measured in a Perkin-Elmer FT-IR 1760X spectrometer. Melting points and results of elemental analyses were uncorrected. Column chromatography was carried out on silica gel [Merck Silica Gel 60 (0.063—0.200 μm), Wako gel C-200, or Fuji Silysia FL60D]. Thin layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, Silica Gel 60 F_{254}). The following abbreviations for solvents and reagents are used; diethyl ether (Et_2O), *tert*-butyl methyl ether (MTBE), *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), ethanol (EtOH), ethyl acetate (EtOAc), methanol (MeOH), tetrahydrofuran (THF), methanol (MeOH), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), dimethoxyethane (DME), acetonitrile (CH_3CN), hexamethylphosphoramide (HMPA), sulfur trioxide/pyridine complex (SO_3-Py), 4-(dimethylamino)pyridine (DMAP), tetrabutylammonium fluoride (TBAF).

7-Hydroxy-11,15-bis-*O*-(*tert*-butyldimethylsilyl)-16-(3-methoxymethyl)phenyl-ω-tetranor-PGE$_1$ Methyl Ester (17) To a stirred solution of 3-(*S*)-*tert*-butyldimethylsilyloxy-1-iodo-4-(3-methoxymethyl)phenyl-1-butene **20** (300 mg, 0.69 mmol) in freshly distilled dry diethyl ether (3 ml) was slowly added *tert*-butyllithium (1.47 M in pentane, 0.95 ml, 1.39 mmol) at −70 °C under argon atmosphere and stirring was continued for 1 h at the same temperature. To the resulting suspension was slowly added lithium 2-thienylcyanocuprate (0.25 M in THF, 3.1 ml, 0.76 mmol). The yellow suspension was stirred for 20 min and then a solution of 4-(*R*)-*tert*-butyldimethylsilyloxy-2-cyclopentenone **16** (147 mg, 0.69 mmol) in THF (1 ml) was added dropwise in 3 min. After being stirred for additional 30 min at −70 °C, the resulting yellowish reaction mixture was treated with methyl 7-oxoheptanoate **21** (121 mg, 0.76 mmol) and then stirred for 90 min and the reaction was quenched with saturated aqueous NH_4Cl. The mixture was vigorously stirred for 30 min without cooling and then extracted with diethyl ether repeatedly. The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, and the organic solvent was removed by evaporation. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 5/1—2/1) to give **17** as colorless oil (119 mg, 25%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.06 (m, 4H), 5.63 (dd, J=15, 6 Hz, 1H), 5.51 (dd, J=15, 8 Hz, 1H), 4.42 (s, 2H), 4.31—4.12 (m, 1H), 4.06—4.01 (m, 1H), 3.72—3.63 (m, 4H), 3.38 (s, 3H), 3.27—3.25 (m, 1H), 2.74 (d, J=6.6 Hz, 2H), 2.70—2.50 (m, 2H), 2.35—2.18 (m, 4H), 2.05—1.97 (m, 1H), 1.70—1.30 (m, 7H), 0.88 (s, 9H), 0.84 (s, 9H), 0.06 (s, 6H), −0.12 (s, 3H), −0.26 (s, 3H).

(7*E*)-7,8-Didehydro-11,15-bis-*O*-(*tert*-butyldimethylsilyl)-16-(3-methoxymethyl)phenyl-ω-tetranor-PGE$_1$ Methyl Ester (18) To a stirred solution of **17** (117 mg, 0.17 mmol) and DMAP (140 mg, 1.1 mmol) in CH_2Cl_2 (2 ml) was added methanesulfonyl chloride (0.04 ml, 0.52 mmol) at 0 °C and the resulting suspension was stirred at the same temperature for 3 h. The reaction mixture was poured into water and extracted with hexane repeatedly. The combined organic layers were washed with brine, dried over Na_2SO_4, and removed by evaporation. The resulting residue was purified by column chromatography on silica gel (EtOAc/hexane, 1/2) to afford **18** as a pale yellow oil. (76 mg, 67%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32—7.00 (m, 4H), 6.71 (td, J=7.5, 1.5 Hz, 1H), 5.51 (dd, J=15.6, 5.7 Hz, 1H), 5.42 (dd, J=15.6, 4.2 Hz, 1H), 4.41 (s, 2H), 4.27—4.21 (m, 1H), 4.09 (d, J=4.8 Hz, 1H), 3.66 (s, 3H), 3.40—3.29 (m, 4H), 2.76—2.62 (m, 2H), 2.43—2.02 (m, 6H), 1.67—1.25 (m, 6H), 0.84 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), −0.14 (s, 3H), −0.23 (s, 3H).

(7*E*)-7,8-Didehydro-16-(3-methoxymethyl)phenyl-ω-tetranor-PGE$_1$ Methyl Ester (19) A solution of **18** (33 mg, 0.049 mmol) and pyridine (0.1 ml) in acetonitrile (1.5 ml) was cooled in an ice-bath and treated with $(HF)_n\cdot$py (Aldrich, 0.2 ml). The reaction mixture was stirred for 90 min without cooling and then slowly poured into a heterogeneous mixture of EtOAc and saturated aqueous $NaHCO_3$ under stirring. The two layers were separated and the aqueous layer was extracted with EtOAc a few times. The combined organic layers were washed with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—0/1) to give **19** as a pale yellow oil (43 mg, 88%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.32—7.07 (m, 4H), 6.75 (td, J=7.8, 2.0 Hz, 1H), 5.63 (dd, J=15.0, 6.0 Hz, 1H), 5.54 (dd, J=15.0, 8.0 Hz, 1H), 4.43—4.35 (m, 3H), 4.19—4.02 (m, 1H), 3.65 (s, 3H), 3.48 (m, 1H), 3.41 (s, 3H), 2.81 (d, J=6.6 Hz, 2H), 2.48 (dd, J=18.0, 5.4 Hz, 1H), 2.34—2.09 (m, 6H), 1.95—1.88 (m, 11H), 1.70—1.23 (m, 6H).

(7*E*)-7,8-Didehydro-16-(3-methoxymethyl)phenyl-ω-tetranor-PGE$_1$ (3) A heterogeneous mixture of **19** (43 mg, 0.10 mmol) and porcine liver esterase (PLE) (Sigma, 20000 U, 0.1 ml) in EtOH (0.5 ml) and phosphate buffer (pH 7.4, 2.5 ml) was stirred for 1.5 h at room temperature. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and the mixture was extracted with EtOAc twice. The organic layer was dried (Na_2SO_4) and concentrated, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 100/1—50/1) to afford **3** as a colorless oil (22 mg, 53%). IR (film) cm^{-1}: 3398, 2930, 2859, 1715, 1645, 1385, 1191, 1091, 1033, 974, 890, 793, 755, 705. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33—7.09 (m, 4H), 6.74 (td, J=7.8, 2.0 Hz, 1H), 5.70—5.56 (m, 2H), 4.53—4.38 (m, 3H), 4.09—4.05 (m, 1H), 3.49—3.43 (m, 1H), 3.42 (s, 3H), 2.89—2.76 (m, 2H), 2.52 (dd, J=18.0, 5.4 Hz, 1H), 2.38—2.06 (m, 7H), 1.67—1.23 (m, 6H). MS (APCI) *m*/*z*: 415 (M−H)$^-$, 397. HR-MS-FAB (*m*/*z*): 415.2118 (Calcd for $C_{24}H_{31}O_6$: 415.2121).

(11*R*,12*R*,13*E*,15*S*)-9-[(Trifluoromethyl)sulfonyloxy]-11,15-bis(*tert*-butyldimethylsilyloxy)-16-(3-methoxymethylphenyl)-17,18,19,20-tetranorprost-8,13-dienoic Acid Methyl Ester (23) To a stirred solution of 3-(*S*)-*tert*-butyldimethylsilyloxy-1-iodo-4-(3-methoxymethyl)phenyl-1-butene **20** (600 mg, 1.4 mmol) in freshly distilled dry Et_2O (6 ml) was slowly added *tert*-butyllithium (1.47 M in pentane, 1.9 ml, 2.8 mmol) at −70 °C under argon atmosphere and stirring was continued for 1 h at the same temperature. To the resulting suspension was added lithium 2-thienylcyanocuprate (0.25 M in THF, 6.6 ml, 1.7 mmol) over 12 min. The resulting yellowish suspension was stirred for 15 min and treated with 4-(*R*)-*tert*-butyldimethylsilyloxy-2-(6-carbomethoxy-2-hexenyl)-2-cyclo-pentenone **22** (492 mg, 1.4 mmol) in THF (2 ml) over 10 min and allowed to warm up to −20 °C over 45 min with stirring. To the resulting yellow solution was added a solution of *N*,*N*-bis(trifluoromethylsulfonyl)aniline (750 mg, 2.1 mmol) in THF (4 ml) and the reaction mixture was allowed to warm up to ambient temperature over 1.5 h. Then the reaction mixture was poured into saturated aqueous $(NH_4)_2SO_4$ solution and extracted with diethyl ether. The organic layer was washed with water, brine and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (30 g, hexane/EtOAc, 10/0—10/1) to afford trifluoromethanesulfonate **23** as a yellow oil (1.1 g). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.12 (m, 4H), 5.58 (dd, J=16, 6 Hz, 1H), 5.36 (dd, J=16, 8 Hz, 1H), 4.43 (s, 2H), 4.28 (m, 1H), 4.05—4.00 (m, 1H), 3.66 (s, 2H), 3.38 (s, 3H), 3.05—2.95 (m, 1H), 2.95—2.85 (m, 1H), 2.80—2.71 (m, 2H), 2.52—2.41 (m, 1H), 2.29 (t, J=7.0 Hz, 2H), 2.3—2.15 (m, 2H), 1.8—1.2 (m, 8H), 0.89 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H), −0.11 (s, 3H), −0.22 (s,

3H).

(11*R*,12*R*,13*E*,15*S*)-11,15-Dihydroxy-16-(3-methoxymethylphenyl)-17,18,19,20-tetranorprost-8,13-dienoic Acid (4) A mixture of **23** (400 mg, <0.49 mmol), formic acid (0.038 ml, 1.0 mmol), triethylamine (0.21 ml, 1.5 mmol), triphenylphosphine (53 mg, 0.2 mmol) and palladium acetate (22 mg, 0.1 mmol) in DMF was stirred at 60 °C for 3 h under argon atmosphere. The resulting solution was cooled to ambient temperature and purified by a short column chromatography on silica gel to remove the residual metal. The collected fractions were concentrated to result in crude olefin as a brown oil.

A solution of the above-described olefin and pyridine (0.3 ml) in CH_3CN (5 ml) was cooled to 0 °C and treated with $(HF)_n \cdot Py$ (0.6 ml). The reaction mixture was stirred for 2 h without cooling and then slowly poured into a heterogeneous stirred mixture of EtOAc and saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc again. The combined organic layers were washed with water, 1 N HCl, water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—0/1) to give an ester as a pale yellow oil (71 mg, <35%).

A heterogeneous mixture of ester (52 mg, <0.13 mmol) and porcine liver esterase (PLE) (Sigma, 20000U, 0.1 ml) in EtOH (5 ml) and phosphate buffer (pH 7.4, 1 ml) was stirred for 2 h at room temperature. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and extracted with EtOAc twice. The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1 and then EtOAc/AcOH, 99/1) to give **4** as a pale brown oil (38 mg, 76%). IR (film) cm^{-1}: 3364, 2928, 2856, 1710, 1447, 1194, 1087, 1033, 971, 791, 756, 703. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.12 (m, 4H), 5.62 (dd, J=16, 6.0 Hz, 1H), 5.41 (dd, J=16, 9.0 Hz, 1H), 5.32 (d, J=1.2 Hz, 1H), 4.43 (s, 2H), 4.38 (m, 1H), 4.12—4.05 (m, 1H), 3.42 (s, 3H), 2.98 (m, 1H), 2.91—2.78 (m, 2H), 2.65 (m, 1H), 2.33 (t, J=7.0 Hz, 2H), 2.26—2.14 (m, 1H), 2.05—1.83 (m, 2H), 1.69—1.52 (m, 2H), 1.50—1.22 (m, 6H). MS (APCI) m/z: 401 $(M-H)^-$. HR-MS-FAB (m/z): 401.2324 (Calcd for $C_{24}H_{33}O_5$: 401.2328).

11-Deoxy-16-(3-methoxymethyl)phenyl-ω-tetranor-5-thiaPGE$_1$ Methyl Ester (25) A solution of **24** (334 mg, 0.74 mmol) in acetic acid (4 ml) and 1 N HCl (0.35 ml) was stirred at 80 °C under argon atmosphere. After being stirred for 5 h, the reaction mixture was allowed to warm up to room temperature, diluted with MTBE, washed with water twice, saturated $NaHCO_3$, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1) to give an enone as a yellow oil (153 mg, 48%). Then to a stirred suspension of $LiAlH_4$ (134 mg, 3.54 mmol) in THF (2 ml) was added a mixture of copper iodide (674 mg, 3.54 mmol) in THF (3 ml) and HMPA (3 ml) at −78 °C under argon atmosphere. To this mixuture was added a solution of above-described enone (153 mg, 0.354 mmol) at −78 °C. After being stirred for 3 h, the reaction was quenched with 2-propanol (1 ml). The reaction mixture was allowed to warm up to room temperature after the addition of saturated aqueous ammonium chloride. The reaction mixture was diluted with THF and EtOAc and filtered through Celite. The filtrate was washed with water, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/2—2/3) to give **25** as a pale yellow oil (113 mg, 74%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.53—7.10 (m, 4H), 5.74—5.62 (m, 2H), 4.44 (s, 2H), 4.36 (m, 1H), 3.68 (s, 3H), 3.41 (s, 3H), 2.9—2.75 (m, 2H), 2.7—2.3 (m, 8H), 2.30—2.00 (m, 3H), 2.04—1.53 (m, 6H).

11-Deoxy-16-(3-methoxymethyl)phenyl-w-tetranor-5-thiaPGE$_1$ (5) A heterogeneous mixture of ester **25** (69 mg, 0.159 mmol) and porcine liver esterase (PLE) (Sigma, 20000U, 197 units/ml, 0.1 ml) in EtOH (1 ml) and phosphate buffer (pH 7.4, 5 ml) was stirred for 2 h at room temperature. The resulting clear solution was poured into saturated aqueous $(NH_4)_2SO_4$ and extracted with EtOAc twice. The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 1/0—40/1) to give **5** as a colorless oil (56 mg, 84%). IR (film) cm^{-1}: 3426, 2927, 1733, 1447, 1406, 1384, 1233, 1193, 1160, 1091, 1031, 973, 914, 793, 705. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.28—7.10 (m, 4H), 5.75—5.61 (m, 2H), 4.45 (s, 2H), 4.44 (m, 1H), 4.00—2.78 (m, 2H), 3.42 (s, 3H), 2.89 (dd, J=14.2, 5.0 Hz, 1H), 2.79 (dd, J=14.2, 8.0 Hz, 1H), 2.68—2.31 (m, 8H), 2.35—2.07 (m, 3H), 1.99—1.51 (m, 5H). MS (APCI) m/z: 419 $(M-H)^-$. HR-MS-FAB (m/z): 421.2073 (Calcd for $C_{23}H_{33}O_5S$: 421.2049).

Ethyl 7-[(2*R*)-2-(*tert*-Butyldimethylsilyloxy)methyl-5-oxo-1-pyrrolidinyl]heptanoate ((*R*)-27) To a stirred solution of (*R*)-**26** (598 mg, 2.61 mmol) in DMF (3 ml) was added sodium hydride (62% in mineral oil, 131 mg, 3.39 mmol) at 0 °C under argon atmosphere. Stirring was continued at room temperature for 1 h, and 60 °C for additional 1 h. To the resulting suspension was added ethyl 7-bromohexanoate (0.61 ml, 3.13 mmol) at 0 °C, and stirring was continued at 80 °C for additional 1.5 h. The resulting pale brown solution was poured into saturated aqueous NH_4Cl, extracted with EtOAc, washed with H_2O, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1) to give (*R*)-**27** as a colorless oil (620 mg, 63%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.11 (q, J=7.2 Hz, 2H), 3.71—3.55 (m, 4H), 3.02—2.90 (m, 1H), 2.50—2.22 (m, 4H), 2.13—1.99 (m, 1H), 1.88—1.86 (m, 1H), 1.66—1.44 (m, 5H), 1.40—1.25 (m, 3H), 1.12 (t, J=7.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

Ethyl 7-[(2*R*)-2-(Hydroxymethyl)-5-oxo-1-pyrrolidinyl]heptanoate ((*R*)-28) A solution of (*R*)-**27** (620 mg, 1.61 mmol) in THF (2.0 ml) was treated with a solution of TBAF (tetrabutylammonium fluoride, 1.0 M in THF, 1.93 ml, 1.93 mmol) at room temperature under argon atmosphere for 1 h. The reaction was quenched with H_2O. The reaction mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (EtOAc) to give (*R*)-**28** as a colorless oil (397 mg, 91%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.12 (q, J=7.2 Hz, 2H), 3.83—3.58 (m, 4H), 3.04—2.93 (m, 1H), 2.55—2.26 (m, 4H), 2.18—2.06 (m, 1H), 2.00—1.78 (m, 1H), 1.72 (bs, 2H), 1.68—1.42 (m, 5H), 1.41—1.22 (m, 6H).

Ethyl 7-[(2*R*)-2-{(1*E*)-4-[3-(Methoxymethyl)phenyl]-3-oxo-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]heptanoate ((*R*)-29) To a stirred solution of the alcohol (396 mg, 1.46 mmol) in EtOAc (3.5 ml) and *N*,*N*-diisopropylethylamine (1.53 ml, 8.79 mmol) was added a solution of SO_3-Py (699 mg, 4.39 mmol) in DMSO (2.5 ml) at 0 °C under argon atmosphere. After being stirred at the same temperature for 20 min, the reaction was quenched with 1 N HCl. The reaction mixture was exracted with EtOAc three times, washed with saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield an aldehyde as a pale yellow oil.

To a stirred solution of dimethy 3-[(3-methoxymethyl)phenyl]-2-oxopropanephosphonate **31** (584 mg, 2.04 mmol) in THF (20 ml) was added sodium hydride (60% in mineral oil, 68.0 mg, 1.75 mmol) in several portions at 0 °C under argon atmosphere. After being stirred at ambient temperature for 90 min, to this stirred suspension was added a solution of the above-described aldehyde in THF (2 ml) at 0 °C and stirring was continued for 2.5 h. The reaction mixture was quenched with acetic acid. The resulting yellow solution was diluted with EtOAc, washed with water, then brine, and dried over $MgSO_4$. The solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—0/1) to give enone (*R*)-**29** as a pale yellow oil (331 mg, 53%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38—7.10 (m, 4H), 6.65 (dd, J=15.6, 7.8 Hz, 1H), 6.22 (dd, J=15.6, 6.6 Hz, 1H), 4.41 (s, 2H), 4.21—4.03 (m, 3H), 3.85 (s, 2H), 3.55 (m, 1H), 3.40 (s, 3H), 2.70 (m, 1H), 2.43—2.19 (m, 5H), 1.83—1.75 (m, 11H), 1.68—1.56 (m, 2H), 1.50—1.18 (m, 9H).

Ethyl 7-[(2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]heptanoate ((*R*)-30) To a stirred solution of (*R*)-**29** (330 mg, 0.77 mmol) in THF (3.9 ml) was added a solution of (*R*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.19 ml, 0.19 mmol) at room temperature under argon atmosphere. To this reaction mixture was added dropwise a solution of borane–THF complex (1.0 M in THF, 0.46 ml, 0.46 mmol) in 5 min. The resulting solution was stirred for 1 h, then treated with MeOH (0.3 ml) and stirring was continued for 5 min. The reaction mixture was diluted with EtOAc, washed with 1 N HCl, water, saturated $NaHCO_3$, brine, and dried over Na_2SO_4. After evaporation, the resulting residue was purified by column chromatography on silica gel (EtOAc/MeOH, 100/0—20/1) to give alcohol (*R*)-**30** as a colorless oil (220 mg, 66%). IR (film) cm^{-1}: 3398, 2931, 2859, 1732, 1665, 1448, 1419, 1375, 1260, 1184, 1099, 1035, 973, 790, 704. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38—7.10 (m, 4H), 5.73 (dd, J=15.3, 6.0 Hz, 1H), 5.50 (dd, J=15.3, 8.0 Hz, 1H), 4.48—4.35 (m, 3H), 4.17—3.98 (m, 3H), 3.53—3.36 (m, 4H), 2.92—2.68 (m, 3H), 2.44—2.05 (m, 6H), 1.81—1.20 (m, 12H).

7-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}-5-oxopyrrolidin-1-yl)heptanoic Acid (6) A solution of (*R*)-**30** (115 mg, 0.266 mmol) in EtOH (0.3 ml), DME (0.1 ml) and 2 N NaOH (0.16 ml) was stirred at ambient temperature for 16 h. After neutralization with 2 N HCl (0.3 ml) under cooling, the reaction mixture was extracted with EtOAc three times, and the organic layer was washed with brine, dried over

Na_2SO_4. The organic solvent was removed by evaporation. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 50/1—20/1) to afford **5** as a colorless oil (104 mg, 98%). IR (film) cm^{-1}: 3410, 2925, 1734, 1693, 1639, 1444, 1405, 1381, 1219, 1157, 1091, 1029, 971, 793, 756, 704. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.36—7.12 (m, 4H), 5.72 (d, J=1.5 Hz, 1H), 5.68—5.64 (m, 2H), 4.47 (s, 2H), 4.46—4.34 (m, 1H), 3.44 (s, 3H), 3.13 (s, 2H), 2.91—2.80 (m, 2H), 2.60—2.30 (m, 4H), 2.23 (d, J=1.5 Hz, 3H), 2.22—2.05 (m, 3H), 2.00—1.78 (m, 2H), 1.75—1.57 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 177.2, 175.1, 138.5, 137.6, 135.5, 130.4, 128.9, 128.8, 128.6, 126.2, 74.7, 72.3, 60.4, 58.3, 43.9, 40.5, 33.8, 30.1, 28.5, 26.9, 26.3, 25.7, 24.5. MS (APCI) m/z: 431 $(M-H)^-$. HR-MS-FAB (m/z): 402.2285 (Calcd for $C_{23}H_{32}NO_5$: 402.2280).

Ethyl 7-[(2*S*)-2-(*t*-Butyldimethylsilyloxy)methyl-5-oxo-1-pyrrolidinyl]-heptanoate ((*S*)-27) Compound (*S*)-**27** was prepared from (*S*)-**26** according to the same procedure as described of (*R*)-**27** from (*R*)-**26** as a pale yellow oil (54% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.11 (q, J=7.2 Hz, 2H), 3.72—3.52 (m, 4H), 2.96 (m, 1H), 2.35—2.28 (m, 2H), 2.04 (m, 1H), 1.81 (m, 1H), 1.72—1.18 (m, 9H), 1.24 (t, J=7.2 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H).

Ethyl 7-[(2*S*)-2-(Hydroxymethyl)-5-oxo-1-pyrrolidinyl]heptanoate ((*S*)-28) Compound (*S*)-**28** was prepared from (*S*)-**27** according to the same procedure as described of (*R*)-**28** from (*R*)-**27** as a pale yellow oil (78% yield). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.12 (q, J=7.2 Hz, 2H), 3.87—3.53 (m, 4H), 2.98 (m, 1H), 2.60—1.84 (m, 7H), 1.80—1.20 (m, 8H), 1.26 (t, J=7.2 Hz, 3H).

Ethyl 7-[(2*S*)-2-{(1*E*)-4-[3-(Methoxymethyl)phenyl]-3-oxo-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]heptanoate ((*S*)-29) Compound (*S*)-**29** was prepared from (*S*)-**28** according to the same procedure as described of (*R*)-**29** from (*R*)-**28** as a pale yellow oil. This crude oil was used for the next reaction without further purification.

Ethyl 7-[(2*S*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]heptanoate ((*S*)-30) Compound (*S*)-**30** was prepared from (*S*)-**29** according to the same procedure as described of (*R*)-**30** from (*R*)-**29** as a colorless oil (42% from (*S*)-**28**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34—7.09 (m, 4H), 5.75 (dd, J=15.5, 5.9 Hz, 1H), 5.47 (ddd, J=15.5, 8.6, 1.4 Hz, 1H), 4.44 (s, 2H), 4.40 (m, 1H), 4.11 (q, J=7.2 Hz, 2H), 4.03 (m, 1H), 3.48 (m, 1H), 3.40 (s, 3H), 2.94—2.72 (m, 3H), 2,44—1.84 (m, 6H), 1.76—1.18 (m, 9H), 1.25 (t, J=7.2 Hz, 3H).

7-((2*S*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}-5-oxopyrrolidin-1-yl)heptanoic Acid (7) Compound **7** was prepared from (*S*)-**30** according to the same procedure as described of **6** from (*R*)-**30** as a pale yellow oil (76% yield). IR (KBr) cm^{-1}: 3403, 2930, 1729, 1660, 1455, 1388, 1265, 1193, 1098, 1036, 973, 792, 704, 667. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34—7.09 (m, 4H), 5.76 (dd, J=15.6, 6.0 Hz, 1H), 5.47 (ddd, J=15.6, 8.7, 1.2 Hz, 1H), 4.45 (s, 2H), 4.40 (m, 1H), 4.03 (m, 1H), 3.50—3.35 (m, 4H), 3.00—2.62 (m, 3H), 2.50—2.02 (m, 6H), 1.78—1.10 (m, 9H); MS (APCI) m/z: 402 $(M-H)^-$. HR-MS-FAB (m/z): 402.2274 (Calcd for $C_{23}H_{32}NO_5$: 402.2280).

Ethyl 7-[(2*R*)-2-(Hydroxymethyl)-1-pyrrolidinyl]-7-oxoheptanoate (33) To a stirred solution of D-prolinol **32** (500 mg, 4.34 mmol) in dioxane (15 ml) and 2 N NaOH (7.4 ml) added a solution of ethyl 6-(chloroformyl)-hexanoate (1.53 g, 7.41 mmol) in dioxane (2 ml) at 0 °C. The reaction mixture was stirred for 30 min, and extracted with EtOAc. The organic layer was washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (EtOAc) to give amide alcohol **33** as a colorless oil (615 mg, 46%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.28 (m, 1H), 4.27—4.19 (m, 3H), 3.71—3.40 (m, 3H), 2.40—2.20 (m, 4H), 2.10—1.78 (m, 4H), 1.75—1.55 (m, 5H), 1.45—1.19 (m, 5H).

7-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}pyrrolidin-1-yl)-7-oxoheptanoic Acid (8) Compound **8** was prepared from **33** according to the same procedure as described of **6** from (*R*)-**28** as a colorless oil (38% from **33**). IR (film) cm^{-1}: 3397, 2932, 1729, 1614, 1454, 1384, 1193, 1094, 1038, 971, 791, 753, 705. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35—7.10 (m, 4H), 5.66—5.40 (m, 2H), 4.67—4.31 (m, 4H), 3.60—2.75 (m, 9H), 2.42—2.13 (m, 4H), 2.12—1.57 (m, 8H), 1.53—1.22 (m, 2H). MS (APCI) m/z: 402 $(M-H)^-$. HR-MS-FAB (m/z): 402.2277 (Calcd for $C_{23}H_{32}NO_5$, 402.2280).

***N*-[2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl]acetamide (35)** To a stirred solution of 2-*N*-acetyl aminoethanol **34** (1.03 g, 10.0 mmol) in CH_2Cl_2 (7 ml) were added 3,4-dihydro-2*H*-pyran (1.00 ml, 11.0 mmol) and *p*-toluenesulfonic acid monohydrate (95.0 mg, 0.50 mmol). After being stirred for 3 h at room temperature, the reaction mixture was quenched with triethylamine and evaporated. The resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 2/1—0/1) to give **35** as a colorless oil (1.90 g, *ca.* 100%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.08 (br s, 1H), 4.60—4.52 (m, 1H), 3.95—3.39 (m, 6H), 2.05—1.42 (m, 9H).

Ethyl 7-[Acetyl(2-hydroxyethyl)amino]heptanoate (36) To a stirred solution of **35** (400 mg, 2.14 mmol) in DMF (5.0 ml) was added sodium hydride (60% dispersion in oil, 124 mg, 3.21 mmol) in one portion at ambient temperature under argon atmosphere and the reaction mixture was stirred for 30 min at 50 °C. The reaction mixture was cooled to room temperature resulting in precipitates. To the resulting suspension was added ethyl 7-bromoheptanoate (0.50 ml, 2.57 mmol) and the mixture was stirred for 6 h at 80 °C. The resulting solution was poured into saturated aqueous ammonium chloride, extracted with EtOAc, washed with H_2O and brine, and dried over anhydrous sodium sulfate. The organic solvent was removed by evaporation to afford **36** as an oily product.

A mixture of **36** and *p*-toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) in EtOH (10 ml) was stirred at room temperature for 2 h under argon atmosphere. After quenching with triethylamine, the resulting mixture was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 1/1—0/1) to yield amide alcohol **37** as a pale yellow oil (278 mg, 50% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.18—4.05 (m, 2H), 3.80—3.62 (m, 2H), 3.52 (t, J=5.0 Hz, 2H), 3.28 (t, J=8.0 Hz, 2H), 2.30 (t, J=7. Two Hz, 2H), 2.13 (s, 3H), 1.65—1.48 (m, 5H), 1.45—1.20 (m, 6H).

7-(Acetyl{(2*E*,4*S*)-4-hydroxy-5-[3-(methoxymethyl)phenyl]pent-2-enyl}amino)heptanoic Acid (9) Compound **9** was prepared from **37** according to the same procedure as described of **6** from (*R*)-**28** as a colorless oil (33% from **37**). IR (film) cm^{-1}: 3417, 2931, 1731, 1714, 1614, 1487, 1454, 1384, 1193, 1097, 1037, 973, 792, 756, 705. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38—7.12 (m, 4H), 5.72—5.59 (m, 2H), 4.48—4.35 (m, 3H), 4.05—3.81 (m, 2H), 3.40 (s, 3H), 3.33—3.24 (m, 1H), 3.20—3.14 (m, 1H), 2.95—2.78 (m, 2H), 2.40—2.30 (m, 2H), 2.09 (s, 3H), 1.70—1.24 (m, 8H). MS (APCI) m/z: 390 $(M-H)^-$. HR-MS-FAB (m/z): 390.2273 (Calcd for $C_{22}H_{32}NO_5$: 390.2280).

(2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-[3-(methoxymethyl)phenyl]-2-pentenoate (39) To a stirred solution of 3-(*S*)-*tert*-butyldimethylsilyloxy-1-iodo-4-(3-methoxymethyl)phenyl-1-butene **38** (800 mg, 1.85 mmol) in MeOH (1.1 ml) were added triethylamine (0.39 ml, 2.8 mmol) and bis(triphenylphosphine)palladium dichloride (65.0 mg, 0.093 mmol) under argon atmosphere, and the reaction vessel was replaced with CO gas repeatedly. After being stirred at 55 °C for 12 h, the reaction mixture was cooled to room temperature. The resulting mixture was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 20/1—10/1) to afford **39** as a yellow oil (611 mg, 91%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.32—7.06 (m, 4H), 6.96 (dd, J=16, 4.6 Hz, 1H), 5.99 (dd, J=16, 1.8 Hz, 1H), 4.46 (m, 1H), 4.43 (s, 2H), 3.73 (s, 3H), 2.83 (dd, J=13, 5.6 Hz, 1H), 2.76 (dd, J=13, 7.3 Hz, 1H), 0.85 (s, 9H), −0.09 (s, 3H), −0.25 (s, 3H).

(2*E*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-[3-(methoxymethyl)phenyl]-2-penten-1-ol (40) To a stirred solution of **39** (237 mg, 0.650 mmol) in CH_2Cl_2 (2 ml) was added a solution of diisobutylaluminium hydride (0.95 m in toluene, 1.37 ml, 1.30 mmol) at −70 °C under argon atmosphere, and stirring was continued at that temperature for 30 min. The reaction mixture was allowed to warm up to −20 °C in 30 min. The reaction was quenched with saturated aqueous Na_2SO_4 at 0 °C, and then dried over anhydrous $MgSO_4$. The filtrate was evaporated to give **40** as a yellow oil (240 mg). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.39 (m, 4H), 5.80—5.59 (m, 2H), 4.43 (s, 2H), 4.29 (m, 1H), 4.10 (d, J=3.0 Hz, 2H), 3.38 (s, 3H), 2.77 (m, 2H), 0.84 (s, 9H), −0.09 (s, 3H), −0.20 (s, 3H).

Ethyl 7-[{(2*E*,4*S*)-4-Hydroxy-5-[3-(methoxymethyl)phenyl]-2-penten-1-yl}(methylsulfonyl)amino]heptanoate (42) To a stirred solution of **40** (240 mg) and triethylamine (0.18 ml, 1.3 mmol) in THF (2 ml) was added methanesulfonyl chloride (0.076 ml, 0.98 mmol) at 0 °C under argon atmosphere. After being stirred at same temperature for 10 min, the reaction mixture was quenched with H_2O, diluted with Et_2O, washed with brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield methanesulfonate as a yellow oil.

To a stirred solution of ethyl 7-methanesulfonamidoheptanoate **43** (212 mg, 0.845 mmol) in DMF (1 ml) was added sodium hydride (63% in mineral oil, 32 mg, 0.85 mmol) in several portions at 0 °C under argon atmosphere, and the suspension was stirred for additional 30 min. To this mixture was added a solution of the crude methane sulfonate in DMF (2 ml) and the resulting mixture was stirred at 0 °C for additional 25 min. The reaction mixture was poured into saturated aqueous NH_4Cl, extracted with Et_2O, washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation to afford **41** as a yellow oil (455 mg).

A solution of **41** (455 mg) in THF (1.5 ml) was treated with a solution of tetrabutylammonium fluoride (1.0 M in THF, 0.98 ml, 0.98 mmol) at room temperature under argon atmosphere for 30 min. The reaction mixture was diluted with Et_2O, washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—1/2) to give **42** as a pale yellow oil (248 mg, 84% from **39**). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.33 (m, 4H), 5.79 (dd, J=16, 5.2 Hz, 1H), 5.68 (dt, J=16, 5.6 Hz, 1H), 4.44 (s, 2H), 4.40 (m, 1H), 4.12 (q, J=7.1 Hz, 2H), 3.82 (d, J=5.6 Hz, 2H), 3.40 (s, 3H), 3.11 (t, J=7.6 Hz, 2H), 2.87 (dd, J=13, 5.3 Hz, 1H), 2.80 (dd, J=13, 7.4 Hz, 1H), 2.78 (s, 3H), 2.29 (t, J=7.3 Hz, 2H), 1.73—1.47 (m, 4H), 1.43—1.19 (m, 4H), 1.25 (t, J=7.3 Hz, 3H).

7-[{(2*E*,4*S*)-4-Hydroxy-5-[3-(methoxymethyl)phenyl]pent-2-enyl}-(methylsulfonyl)amino]heptanoic Acid (10) A solution of **42** (226 mg, 0.47 mmol) in MeOH (5 ml) and 2 N NaOH (2.5 ml) was stirred at ambient temperature for 1.5 h. After acidification with 2 N HCl (3.0 ml) under cooling, the reaction mixture was extracted with EtOAc three times, washed with brine, and dried over Na_2SO_4. The combined organic layers were evaporated to give a crude mixture, which was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 30/1—20/1) to afford **10** as a pale yellow oil (209 mg, 99%). IR (film) cm^{-1}: 3430, 2932, 2862, 1731, 1714, 1449, 1412, 1384, 1327, 1148, 1094, 1035, 967, 785, 705, 518. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33—7.09 (m, 4H), 5.79 (dd, J=15, 5.6 Hz, 1H), 5.69 (dt, J=15, 6.0 Hz, 1H), 4.45 (s, 2H), 4.41 (m, 1H), 3.82 (d, J=6.0 Hz, 2H), 3.41 (s, 3H), 3.12 (t, J=7.5 Hz, 2H), 2.87 (dd, J=14, 5.1 Hz, 1H), 2.79 (dd, J=14, 7.8 Hz, 1H), 2.78 (s, 3H), 2.33 (t, J=7.2 Hz, 2H), 1.70—1.49 (m, 4H), 1.42—1.22 (m, 4H). MS (APCI) m/z: 426 $(M-H)^-$. HR-MS-FAB (m/z): 426.1937 (Calcd for $C_{21}H_{32}NO_6S$, 426.1950).

Methyl 7-Hydroxy-5-heptynoate (45) To a stirred solution of 5-hexynic acid **44** (1.12 g, 10.0 mmol) in THF (5 ml) was added a solution of ethylmagnesium bromide (1.02 M in THF, 20 ml, 20.4 mmol) at 0 °C under argon atmosphere. After being stirred at room temperature for 1 h, the resulting gray suspension was treated with paraformaldehyde (600 mg) and the reaction mixture was refluxed for additional 4 h. After being cooled to room temperature, the reaction mixture was poured into 1 N HCl, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. The organic layer was evaporated to afford an oily product, which was dissolved in MeOH (5 ml) and treated with a solution of trimethylsilyldiazomethane (2.0 M in hexane, 3.0 ml). The resulting mixture was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 4/1—1/1) to yield **45** (940 mg, 60%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.24 (dt, J=6.2 Hz, 2H), 3.69 (s, 3H), 2.44 (t, J=7.0 Hz, 2H), 2.30 (tt, J=7.0, 2.0 Hz, 2H), 1.90—1.75 (m, 2H), 1.56 (t, J=6.0 Hz, 1H).

Methyl 7-{(2*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-5-oxo-1-pyrrolidinyl}-5-heptynoate (47) To a stirred solution of **45** (340 mg, 2.18 mmol) and triphenylphosphine (680 mg, 2.60 mmol) in CH_2Cl_2 (5 ml) was added tetrabromomethane (860 mg, 2.60 mmol) at 0 °C under argon atmosphere. After being stirred for 30 min, the reaction was quenched with MeOH. The resulting mixture was diluted with EtOAc, washed with water twice, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 9/1) to give a bromide **46** as a colorless oil (330 mg, 69%).

To a stirred solution of (*R*)-**26** (330 mg, 1.50 mmol) in DMF (6 ml) was added sodium hydride (62.7% in oil dispersion, 57.0 mg, 1.50 mmol) at room temperature under argon atmosphere. Stirring was continued for 30 min to result in precipitates. To the resulting suspension was added a solution of the bromide **46** (330 mg, 1.50 mmol) in DMF (1 ml), and stirring was continued for additional 1 h. The resulting pale brown solution was poured into saturated aqueous NH_4Cl, extracted with EtOAc, washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 4/1—1/1) to give **47** as a pale yellow oil (418 mg, 78%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.58 (dt, J=16.6, 3.0 Hz, 1H), 3.93—3.80 (m, 1H), 3.75 (dd, J=11.2, 4.0 Hz, 1H), 3.68 (s, 3H), 3.75—3.61 (m, 2H), 2.55—2.32 (m, 4H), 2.24 (tt, J=6.6, 3.0 Hz, 2H), 2.25—2.05 (m, 1H), 1.95—1.75 (m, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

Methyl (5*Z*)-7-[(2*R*)-2-{(1*E*)-4-[3-(Methoxymethyl)phenyl]-3-oxo-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]-5-heptenoate (48) A solution of **47** (418 mg, 1.17 mmol) in benzene/cyclohexane/cyclohexene (5 ml/5 ml/1 ml) was vigorously stirred under hydrogen atmosphere in the presence of Lindlar catalyst (50 mg) for 1.5 h. The catalyst was removed by filtration. The filtrate was evaporated to dryness. The resulting residue was treated with *p*-toluenesulfonic acid monohydrate (46 mg, 0.24 mmol) in MeOH (6 ml) at room temperature for 4 h. The reaction mixture was treated with triethylamine, and concentrated to give an alcohol as a colorless oil. To a stirred solution of the alcohol in CH_2Cl_2 (2 ml), DMSO (2 ml) and triethylamine (0.98 ml, 7.0 mmol) was added SO_3·Py (560 mg, 3.50 mmol) at 0 °C under argon atmosphere. After being stirred at the same temperature for 30 min, the reaction was quenched with H_2O. The reaction mixture was diluted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield an aldehyde as a yellow oil.

To a stirred solution of dimethyl 3-[(3-methoxymethyl)phenyl]-2-oxopropanephosphonate **31** (470 mg, 1.64 mmol) in THF (12 ml) was added sodium hydride (62.7% in mineral oil, 54.0 mg, 1.40 mmol) in several portions at 0 °C under argon atmosphere and stirring was further continued at ambient temperature for 90 min. To the stirred suspension was added a solution of the above-described aldehyde (392 mg, 1.46 mmol) in THF (2 ml) at 0 °C and stirring was continued for 1 h. The reaction was quenched with acetic acid, diluted with EtOAc, washed with water, then brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (EtOAc) to give an enone **48** as a pale yellow oil (313 mg, 66% in 4 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40—7.15 (m, 4H), 6.68 (dd, J=16.0, 8.0 Hz, 1H), 6.21 (d, J=16.0 Hz, 1H), 5.55—5.45 (m, 1H), 5.30—5.23 (m, 1H), 4.43 (s, 2H), 4.25—4.11 (m, 2H), 3.84 (s, 2H), 3.68 (s, 3H), 3.45—3.35 (m, 1H), 3.39 (s, 3H), 2.51—2.22 (m, 5H), 2.05—1.91 (m, 2H), 1.85—1.55 (m, 3H).

(5*Z*)-7-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}-5-oxopyrrolidin-1-yl)hept-5-enoic Acid (11) Compound **11** was prepared from **48** according to the same procedure as described for the preparation of **6** from (*R*)-**29** as a colorless oil (46% from **48**); IR (film) cm^{-1}: 3396, 2929, 1726, 1661, 1449, 1420, 1243, 1190, 1097, 1036, 973, 790, 756, 704. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32—7.11 (m, 4H), 5.70 (dd, J=16, 5 Hz, 1H), 5.60—5.48 (m, 2H), 5.34—5.25 (m, 1H), 4.44 (s, 2H), 4.50—4.39 (m, 1H), 4.20 (dd, J=15, 5.0 Hz, 1H), 4.03 (dt, J=8.0, 6.2 Hz, 1H), 3.49 (dd, J=15, 8.0 Hz, 1H), 3.42 (s, 3H), 2.92—2.78 (m, 2H), 2.50—2.05 (m, 7H), 1.77—1.61 (m, 3H). MS (APCI) m/z: 400 $(M-H)^-$. HR-MS-FAB (m/z): 400.2130 (Calcd for $C_{23}H_{30}NO_5$: 400.2124).

{(2*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-5-oxo-1-pyrrolidinyl}acetate (49) To a stirred solution of (*R*)-**26** (300 mg, 1.31 mmol) in DMF (5 ml) was added sodium hydride (60% in mineral oil, 60 mg, 1.57 mmol) at room temperature under argon atmosphere, and then stirring was continued at 50 °C for 30 min. To the stirred suspension was added methyl bromoacetate (0.19 ml, 1.96 mmol) at 0 °C and stirring was continued at 50 °C for additional 1 h. After being cooled to room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc three times. The combined organic layers were washed with H_2O twice, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc 3/2) to give an ester **49** as a colorless oil (241 mg, 61%). ^{1}H-NMR (200 MHz $CDCl_3$) δ: 4.47 (d, J=17.6 Hz, 1H), 3.95 (d, J=17.6 Hz, 1H), 3.92—3.74 (m, 1H), 3.72 (s, 3H), 3,74—3.56 (m, 2H), 2.60—2.35 (m, 2H), 2.35—2.05 (m, 1H), 1.80—1.60 (m, 1H), 0.87 (s, 9H), 0.04 (s, 6H).

(5*R*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-1-(2-hydroxyethyl)-2-pyrrolidinone (50) To a stirred solution of **49** (240 mg, 0.796 mmol) in MeOH (5 ml) was added sodium borohydride (450 mg, 11.9 mmol) at 0 °C under argon atmosphere. After being stirred at room temperature for 3 h, the reaction was quenched with H_2O. The reaction mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, and dried over $MgSO_4$. Removal of the solvent by evaporation gave an alcohol **50** as a colorless oil (225 mg, >100%). ^{1}H-NMR (200 MHz $CDCl_3$) δ: 3.90—3.66 (m, 3H), 3.77 (dd, J=10.5, 3.3 Hz, 1H), 3.61 (dd, J=10.5, 4.2 Hz, 1H), 3.58—3.40 (m, 3H), 2.49 (ddd, J=17.1, 10.2, 7.2 Hz, 1H), 2.35 (ddd, J=17.1, 10.2, 5.1 Hz, 1H), 2.22—2.04 (m, 1H), 1.92—1.79 (m, 1H), 1.62 (br s, 1H), 0.89 (s, 9H), 0.07 (s, 6H).

***S*-(2-{(2*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-5-oxo-1-pyrrolidinyl}ethyl)ethanethioate (51)** To a stirred solution of **50** (225 mg, 0.796 mmol) in THF (3 ml) and *N*,*N*-diisopropylethylamine (0.34 ml, 1.97 mmol) was added methanesulfonyl chloride (0.076 ml, 0.987 ml) at 0 °C under argon atmosphere. Stirring was continued at room temperature for 2 h. To the reaction mixture was added potassium carbonate (341 mg, 2.47 mmol) and a solution of potassium thioacetate (188 mg, 1.65 mmol) in DMF (5 ml) and the stirring was continued at 50 °C for additional 90 min. After being cooled to room temperature, the reaction was quenched with 1 N HCl. The reaction mixture was extracted with EtOAc twice. The combined organic layers were washed with H_2O twice, brine, and dried over $MgSO_4$.

The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1) to afford a thioacetate **51** as a pale brown oil (186 mg, 71% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.81 (m, 1H), 3.78—3.62 (m, 2H), 3.62 (m, 1H), 3.23 (m, 1H), 3.14—2.94 (m, 2H), 2.45 (m, 1H), 2.34 (s, 3H), 2.28 (m, 1H), 2.16—2.02 (m, 1H), 1.85 (m, 1H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

Methyl 4-[(2-{(2*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoate (49) To a stirred solution of thioacetate **51** (186 mg, 0.561 mmol) in MeOH (4 ml) was added potassium carbonate (186 mg, 1.35 mmol) and methyl 4-iodobutyrate (172 mg, 0.673 mmol) at 0 °C under argon atmosphere. After being stirred at room temperature for 2 h, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc, washed with H_2O twice, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1) to give a sulfide **52** as a yellow oil (206 mg, 94%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.85—3.66 (m, 3H), 3.68 (s, 3H), 3.58 (m, 1H), 3.23 (m, 1H), 2.80—2.56 (m, 4H), 2.50—2.24 (m, 2H), 2.44 (t, J=7.5 Hz, 2H), 2.10 (m, 1H), 1.95—1.84 (m, 2H), 1.86 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

Methyl 4-({2-[(2*R*)-2-{(1*E*)-4-[3-(Methoxymethyl)phenyl]-3-oxo-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]ethyl}thio)butanoate (53) A solution of sulfide **52** (206 mg, 0.529 mmol) in THF (3 ml) was treated with tetraammonium fluoride (1.00 ml, 1 M in THF, 1.00 mmol) at room temperature under argon atmosphere for 1 h. After addition of brine, the reaction mixture was extracted with EtOAc repeatedly (×6). The combined oganic layers were dried over $MgSO_4$, and concentrated to give a crude alcohol (233 mg).

To a stirred solution of the alcohol (233 mg) in EtOAc (3 ml) and *N*,*N*-diisopropylethylamine (0.55 ml, 3.17 mmol) was added a solution of SO_3-Py (252 mg, 1.59 mmol) in DMSO (3 ml) at 0 °C under argon atmosphere. After being stirred at the same temperature for 30 min, the reaction was quenched with 1 N HCl. The reaction mixture was diluted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield an aldehyde as a yellow oil. To a stirred solution of dimethyl 3-[(3-methoxymethyl)phenyl]-2-oxopropanephosphonate **31** (380 mg, 0.793 mmol) in THF (12 ml) was added sodium hydride (62.7% in mineral oil, 24 mg, 0.634 mmol) in several portions at 0 °C under argon atmosphere and stirring was further continued at ambient temperature for 90 min. To the stirred suspension was added a solution of the above-described aldehyde in THF (5 ml) at 0 °C and stirring was continued at room temperature for 30 min. The reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with EtOAc, washed with water, then brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (EtOAc) to give an enone **53** as a pale yellow oil (109 mg, 48% in 3 steps). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.10 (m, 4H), 6.67 (dd, J=15.8, 8.0 Hz, 1H), 6.24 (d, J=15.8 Hz, 1H), 4.45 (s, 2H), 4.35—4.20 (m, 1H), 4.00—3.60 (m, 4H), 3.68 (s, 3H), 3.40 (s, 3H), 3.05—2.85 (m, 1H), 2.70—2.10 (m, 9H), 2.00—1.70 (m, 2H).

4-{[2-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}-5-oxopyrrolidin-1-yl)ethyl]sulfanyl}butanoic Acid (12) Compound **12** was prepared from **53** according to the same procedure as described for the preparation of **6** from (*R*)-**29** as a colorless oil (78% from **53**); IR (film) cm^{-1}: 3398, 2925, 1726, 1660, 1447, 1419, 1383, 1236, 1159, 1096, 1035, 974, 914, 791, 731, 704, 667, 569. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.10 (m, 4H), 5.79 (dd, J=15.4, 5.2 Hz, 1H), 5.54 (dd, J=15.4, 8.4 Hz, 1H), 4.50—4.40 (m, 1H), 4.46 (s, 2H), 4.20—4.05 (m, 1H), 3.70—3.50 (m, 1H), 3.42 (s, 3H), 3.10 (m, 1H), 2.90—2.80 (m, 2H), 2.80—2.10 (m, 9H), 2.00—1.60 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 175.5, 175.4, 138.4, 137.6, 135.9, 130.1, 129.0, 128.8, 128.7, 126.3, 74.7, 72.1, 60.9, 58.3, 43.7, 40.3, 32.5, 30.9, 30.0, 29.3, 25.9, 24.8. MS (APCI) *m*/*z*: 420 $(M-H)^-$. HR-MS-FAB (*m*/*z*): 420.1839 (Calcd for $C_{22}H_{30}NO_5S$: 420.1845).

***tert*-Butyl (2*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-5-oxo-1-pyrrolidinecarboxylate (54)** To a stirred solution of (*R*)-**26** (300 mg, 1.30 mmol) in THF (2.5 ml) and DMAP (16 mg, 0.131 mmol) was added di-*tert*-butyl dicarbonate (0.60 ml, 2.62 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 90 min, diluted with EtOAc, washed with H_2O, and dried over Na_2SO_4. The organic solvent was removed by evaporation to give **54** (385 mg) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.18 (m, 1H), 3.91 (dd, J=10.2, 3.9 Hz, 1H), 3.67 (dd, J=10.2, 2.4 Hz, 1H), 2.70 (m, 1H), 2.36 (m, 1H), 2.17—1.96 (m, 2H), 1.52 (s, 9H), 0.87 (s, 9H), 0.04 (s, 6H).

***tert*-Butyl (2*R*)-2-(Hydroxymethyl)-5-oxo-1-pyrrolidinecarboxylate (55)** A solution of **54** (385 mg, 1.30 mmol) in THF (1 ml) was treated with a solution of TBAF (1.0 M in THF, 1.56 ml, 1.56 mmol) at room temperature under argon atmosphere for 90 min. The reaction mixture was diluted with $CHCl_3$, washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (EtOAc/MeOH, 1/0—95/5) to give **55** as a pale yellow oil (209 mg, 75% in 3 steps). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.30—4.19 (m, 1H), 3.93—3.69 (m, 2H), 2.70 (m, 1H), 2.55—1.85 (m, 4H), 1.70—1.45 (m, 1H).

***tert*-Butyl (2*R*)-2-{(1*E*)-4-[3-(Methoxymethyl)phenyl]-3-oxo-1-buten-1-yl}-5-oxo-1-pyrrolidinecarboxylate (56)** To a stirred solution of **55** (209 mg, 0.972 mmol) in EtOAc (5 ml) DMSO (1.6 ml) and propylethylamine (1.02 ml, 6.0 mmol) was added SO_3-Py (465 mg, 2.92 mmol) at 0 °C under argon atmosphere. After being stirred at the same temperature for 20 min, the reaction was quenched with H_2O. The reaction mixture was diluted with $CHCl_3$, washed with 1 N HCl, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield an aldehyde as a yellow oil.

To a stirred solution of dimethyl 3-[(3-methoxymethyl)phenyl]-2-oxopropanephosphonate **31** (390 mg, 1.36 mmol) in THF (14 ml) was added sodium hydride (62% in mineral oil, 46.0 mg, 1.17 mmol) at 0 °C under argon atmosphere and stirring was further continued at ambient temperature for 90 min. To the stirred suspension was added a solution of the above-described aldehyde in THF (2 ml) at 0 °C and stirring was continued for 1 h. The reaction was quenched with acetic acid. The reaction mixture was diluted with EtOAc, washed with water, then brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 2/1—0/1) to give an enone **56** as a pale yellow oil (195 mg, 52% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39—7.10 (m, 4H), 6.83 (dd, J=15.6, 6.0 Hz, 1H), 6.21 (dd, J=15.6, 1.2 Hz, 1H), 4.74 (m, 1H), 4.43 (m, 1H), 3.83 (s, 2H), 3.39 (s, 3H), 2.59—2.40 (m, 2H), 2.29 (m, 1H), 1.79 (m, 1H), 1.41 (s, 9H).

***tert*-Butyl (2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinecarboxylate (57)** To a stirred solution of an enone **56** (208 mg, 0.554 mmol) in THF (3 ml) was added a solution of (*R*)-2-methyl-CBS-oxazaborolidine (1.0 m in toluene, 0.139 ml, 0.139 mmol) at room temperature under argon atmosphere. To the reaction mixture was added dropwise a solution of borane–THF complex (1.0 M in THF, 0.333 ml, 0.333 mmol) in 5 min. The resulting solution was stirred for 1 h, then treated with MeOH (0.4 ml) and stirring was continued for 5 min. The reaction mixture was diluted with EtOAc, washed with 1 N HCl, water, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. After evaporation, the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—0/1) to give an alcohol **57** as a colorless oil (120 mg, 58%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.36—7.10 (m, 4H), 5.74—5.69 (m, 2H), 4.69—4.61 (m, 1H), 4.44 (s, 2H), 4.41 (m, 1H), 3.41 (s, 3H), 2.90—2.73 (m, 2H), 2.60—2.38 (m, 2H), 2.26 (m, 1H), 1.78 (m, 1H), 1.51 (s, 9H).

(5*R*)-5-{(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-[3-(methoxymethyl)-phenyl]-1-buten-1-yl}-2-pyrrolidinone (59) To a stirred solution of an alcohol **57** (2.89 g, 7.70 mmol) in DMF (70 ml) and imidazole (629 mg, 9.24 mmol) was added *tert*-butyldimethylsilyl chloride (1.22 g, 8.09 mmol) at room temperature under argon atmosphere. After being stirred for 1 h, the reaction mixture was diluted with EtOAc, washed with H_2O twice, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give **58** as a yellow oil. To a stirred solution of **58** in MeOH (10 ml) was added a solution of magnesium methoxide (0.93 M in MeOH, 41.4 ml, 38.5 mmol) at room temperature. After being stirred for 1 h, the reaction was quenched with acetic acid. The reaction mixture was diluted with EtOAc and successively washed with H_2O, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—0/1) to give **59** as a colorless oil (2.14 g, 71% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.05 (m, 4H), 5.72—5.58 (m, 2H), 5.34 (m, 1H), 4.47—4.36 (m, 2H), 4.24 (m, 1H), 4.10 (m, 1H), 3.42 (s, 3H), 2.84—2.68 (m, 2H), 2.36—2.20 (m, 3H), 1.74 (m, 1H), 0.85 (s, 9H), −0.04 (s, 3H), −0.14 (s, 3H).

(4*S*)-6-(*tert*-Butyldimethylsilyloxy)-4-methylhexanal (66) To a stirred solution of (−)-β-citronellol (5.00 g, 32.0 mmol) was added *tert*-butyldimethylsilyl chloride (5.31 g, 35.2 mmol) and imidazole (2.83 g, 61.6 mmol) in DMF (80 ml) at 0 °C under argon atmosphere. After being stirred at room temperature for 30 min, the reaction was quenched with H_2O. The reaction mixture was diluted with EtOAc, and washed with saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The organic solvent was re-

moved by evaporation to give a TBS ether as a yellow oil.

A stirred solution of the above-described ether in MeOH (70 ml) and CH_2Cl_2 (70 ml) was cooled to −78 °C. Gaseous ozone was bubbled through the reaction mixture at the same temperature for 3 h. The reaction mixture was treated with dimethyl sulfide (2.95 ml, 40 mmol) and then warmed up to 0 °C in 1 h. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 20/1) to give an aldehyde **66** as a colorless oil (5.20 g, 70% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.78 (t, J=1.8 Hz, 1H), 3.72—3.59 (m, 2H), 2.51—2.38 (m, 2H), 1.76—1.35 (m, 5H), 0.93—0.87 (m, 12H), 0.04 (s, 6H).

(4*S*)-6-(*tert*-Butyldimethylsilyloxy)-4-methyl-1-hexanol (67) To a stirred solution of **63** (4.37 g, 16.2 mmol) in MeOH (30 ml) was added sodium borohydride (307 mg, 8.10 mmol) at 0 °C under argon atmosphere, and the stirring was continued at room temperature for 1 h. The reaction was quenched with H_2O. The reaction mixture was diluted with EtOAc, and successively washed with 2 N HCl, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 4/1) to give an alcohol **67** as a colorless oil (3.16 g, 72%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.72—3.58 (m, 4H), 1.70—1.09 (m, 8H), 0.98—0.72 (m, 12H), 0.05(s, 3H), 0.02 (s, 3H).

(5*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methylheptanenitrile (68) To a stirred solution of an alcohol **67** (700 mg, 2.84 mmol) in pyridine (5 ml) was added *p*-toluenesulfonyl chloride (1.10 g, 5.68 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred for 1 h, diluted with EtOAc, washed with 1 N HCl, H_2O, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give a *p*-toluenesulfonate. To a stirred solution of a *p*-toluenesulfonate in DMSO (5 ml) was added sodium cyanide (209 mg, 4.26 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 30 min, then cooled to room temperature, diluted with EtOAc, and washed with H_2O three times, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give **68** as a pale yellow oil (674 mg, 93%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.64 (dt, J=7.4, 2.4 Hz, 2H), 2.33 (t, J=7.4 Hz, 2H), 1.80—1.20 (m, 7H), 0.91 (d, J=7.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

(5*S*)-7-Hydroxy-5-methylheptanenitrile (69) A solution of **68** (495 mg, 1.94 mmol) in THF (5 ml) was treated with a solution of tetrabutylammonium fluoride (1.0 M in THF, 3.88 ml, 3.88 mmol) at room temperature under argon atmosphere for 1 h. The reaction mixture was diluted with EtOAc, and washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—1/2) to give **69** as a colorless oil (210 mg, 77%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.80—3.60 (m, 2H), 2.34 (t, J=7.2 Hz, 2H), 1.80—1.10 (m, 8H), 0.93 (d, J=6.6 Hz, 3H).

Methyl (5*S*)-7-Hydroxy-5-methylheptanoate (70) A solution of **69** (210 mg, 1.49 mmol) in EtOH (10 ml) and 12 N potassium hydroxide (5 ml) was refluxed for 4 h. After being cooled to room temperature, the reaction was quenched with H_2O. The reaction mixture was washed with Et_2O. The aqueous layer was acidified with 2 N HCl (30 ml), extracted with EtOAc three times, and washed with brine, and dried over $MgSO_4$. The combined organic layers were evaporated to afford an oily product, which was dissolved in Et_2O (5 ml) and treated with a solution of diazomethane in Et_2O. The resulting mixture was evaporated to give **70** (236 mg, 91%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.80—3.60 (m, 2H), 3.67 (s, 3H), 2.30 (t, J=7.5 Hz, 2H), 1.80—1.10 (m, 8H), 0.91 (d, J=6.6 Hz, 3H).

Methyl (5*S*)-7-Iodo-5-methylheptanoate (60) To a stirred solution of **70** (100 mg, 0.574 mmol) in CH_2Cl_2 (3 ml) and triethylamine (0.12 ml, 0.861 mmol) was added methanesulfonyl chloride (0.053 ml, 0.689 mmol) at 0 °C under argon atmosphere. Stirring was continued for 45 min, the reaction was quenched with saturated aqueous NH_4Cl and the reaction mixture was diluted with EtOAc, and successively washed with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give a methanesulfonate. To a stirred solution of a methanesulfonate in acetone (6 ml) was added sodium iodide (387 mg, 2.58 mmol) at room temperature under argon atmosphere, and stirring was continued at 45 °C for 6 h. The resulting yellow solution was diluted with EtOAc, and washed with water, then brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to afford **60** as a yellow oil (109 mg, 67%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.67 (s, 3H), 3.30—3.10 (m, 2H), 2.30 (t, J=7.5 Hz, 2H), 1.87 (m, 1H), 1.80—1.50 (m, 3H), 1.45—1.10 (m, 3H), 0.89 (d, J=6.3 Hz, 3H).

Methyl (5*S*)-7-[(2*R*)-2-{(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]-5-methylheptanoate (63) To a stirred solution of **59** (130 mg, 0.334 mmol) in DMF (3 ml) was added sodium hydride (62% in mineral oil, 15.0 mg, 0.40 mmol) at room temperature under argon atmosphere. Stirring was continued for 30 min. To the resulting suspension was added a solution of the iodide **60** (104 mg, 0.367 mmol) in DMF (3 ml), and stirring was continued at 50 °C for additional 2 h. The resulting pale brown solution was poured into saturated aqueous NH_4Cl, extracted with EtOAc, washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/1—1/2) to give **63** as a pale yellow oil (126 mg, 69%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.05 (m, 4H), 5.67 (dd, J=15.3, 5.7 Hz, 1H), 5.40 (ddd, J=15.3, 8.4, 1.2 Hz, 1H), 4.42 (s, 2H), 4.35 (m, 1H), 4.00 (m, 1H), 3.66 (s, 3H), 3.70—3.55 (m, 1H), 3.38 (s, 3H), 2.80—2.60 (m, 3H), 2.50—2.10 (m, 5H), 1.75—1.10 (m, 9H), 0.95—0.85 (m, 3H), 0.83 (s, 9H), −0.10 (s, 3H), −0.21 (s, 3H).

(5*S*)-7-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}-5-oxopyrrolidin-1-yl)-5-methylheptanoic Acid (13) A solution of **63** (126 mg, 0.231 mmol) in THF (3 ml) was treated with a solution of TBAF (1.0 M in THF, 2.1 ml, 2.1 mmol) at room temperature under argon atmosphere for 6 h. The reaction mixture was diluted with EtOAc, washed with H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 1/0—20/1) to give an ester as a pale yellow oil (85 mg, 86%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.10 (m, 4H), 5.76 (dd, J=15.2, 5.4 Hz, 1H), 5.53 (dd, J=15.2, 8.4 Hz, 1H), 4.50—4.30 (m, 1H), 4.44 (s, 2H), 4.06 (m, 1H), 3.66 (s, 3H), 3.55 (m, 1H), 3.41 (s, 3H), 3.00—2.70 (m, 3H), 2.50—2.10 (m, 5H), 2.00—1.00 (m, 9H), 0.90 (d, J=6.2 Hz, 3H).

A solution of the above-described ester (55 mg, 0.127 mmol) in MeOH (4 ml) and 2 N NaOH (1 ml) was stirred at room temperature for 3 h. After acidification with 2 N HCl (2 ml) under cooling, the reaction mixture was extracted with EtOAc three times, and the organic layer was washed with brine, and dried over Na_2SO_4. The combined organic layers were evaporated. The resulting residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 20/1—10/1) to afford **13** as a pale yellow oil (54 mg, 100%). IR (film) cm^{-1}: 3376, 2927, 1726, 1656, 1458, 1421, 1380, 1257, 1189, 1159, 1105, 1038, 973, 789, 703, 618. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.10 (m, 4H), 5.78 (dd, J=15.2, 5.2 Hz, 1H), 5.55 (dd, J=15.2, 8.4 Hz, 1H), 4.41 (m, 1H), 4.46 (s, 2H), 4.03 (m, 1H), 3.55 (m, 1H), 3.42 (s, 3H), 3.00—2.70 (m, 4H), 2.50—2.10 (m, 5H), 1.80—1.00 (m, 8H), 0.91 (d, J=5.8 Hz, 3H). MS (APCI) m/z: 416 $(M-H)^-$. HR-MS-FAB (m/z): 416.2446 (Calcd for $C_{24}H_{34}NO_5$: 416.2437).

(5*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methyl-2-heptanone (71) To a stirred solution of the alcohol **67** in EtOAc (10 ml) and *N*,*N*-diisopropylethylamine (4.96 ml, 28.5 mmol) was added a solution of SO_3-Py (2.27 g,14.2 mmol) in DMSO (10 ml) at 0 °C under argon atmosphere. After being stirred at the same temperature for 30 min, the reaction was quenched with H_2O. The reaction mixture was diluted with EtOAc, washed with 1 N HCl, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield an aldehyde as a colorless oil(1.08 g, 93%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 9.78 (t, J=1.8 Hz, 1H), 6.65 (td, J=6.2, 3.0 Hz, 2H), 2.50—2.40 (m, 2H), 1.80—1.20 (m, 6H), 0.90—0.80 (m, 2H), 0.81 (s, 9H), 0.04 (s, 6H).

To a stirred solution of the above-described aldehyde (1.08 g, 4.75 mmol) in THF (10 ml) was added a solution of methylmagnesium bromide (0.93 M in THF, 7.70 ml, 7.12 mmol) at 0 °C under argon atmosphere. After being stirred at the same temperature for 15 min, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with EtOAc, washed with H_2O, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield an alcohol as a colorless oil (1.11 g, 96%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.75 (m, 1H), 3.66 (m, 2H), 1.80—1.10 (m, 7H), 1.19 (d, J=6.3 Hz, 3H), 1.00—0.80 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

To a stirred solution of the above-described alcohol (1.11 g, 4.26 mmol) in EtOAc (10 ml) and *N*,*N*-diisopropylethylamine (4.45 ml, 25.6 mmol) was added a solution of SO_3-Py (2.00 g,12.8 mmol) in DMSO (10 ml) at 0 °C under argon atmosphere. After being stirred at the same temperature for 60 min, the reaction was quenched with H_2O. The reaction mixture was diluted with EtOAc, washed with 1 N HCl, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10/1) to give **71** as a colorless oil (760 mg, 69% from **67**). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.70—3.60 (m, 2H), 2.50—2.40 (m, 2H), 2.14 (s, 3H), 1.80—1.20 (m, 5H), 0.95—0.85 (m, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

Methyl (5*R*)-5-Methyl-8-oxononanoate (72) A solution of **71** (640 mg, 2.48 mmol) in THF (3 ml) was treated with a solution of tetrabutylammonium fluoride (1.0 M in THF, 4.95 ml, 4.95 mmol) at room temperature under argon atmosphere for 1 h. The reaction mixture was diluted with EtOAc, and successively washed with saturated aqueous NH_4Cl, H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation, and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 1/2) to give an alcohol as a colorless oil (297 mg, 83%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.80—3.60 (m, 2H), 2.55—2.40 (m, 2H), 2.15 (s, 3H), 1.80—1.20 (m, 5H), 0.91 (d, J=6.6 Hz, 3H).

To a stirred solution of the above-described alcohol (297 mg, 2.06 mmol) in CH_2Cl_2 (20 ml) was added Celite (3.1 g) and pyridinium chlorochromate (3.10 g, 14.4 mmol) at room temperature under argon atmosphere. After being vigorously stirred for 90 min, Celite was removed by filtration and the filtrate was evaporated to afford an aldehyde.

To a stirred solution of methyl diethylphosphonoacetate (649 mg, 3.09 mmol) in THF (5 ml) was added sodium hydride (60% in mineral oil, 86.0 mg, 2.27 mmol) in several portions at room temperature under argon atmosphere. After being stirred at ambient temperature for 2 h, the stirred suspension was treated with a solution of the above-described aldehyde (392 mg, 1.46 mmol) in THF (5 ml) at −20 °C and stirring was continued for 20 min, and at 0 °C for additional 40 min. The reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with EtOAc, washed with water, then brine, and dried over $MgSO_4$. The solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 3/1—2/1) to give an ester as a pale yellow oil (335 mg, 82% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.92 (dt, J=15.6, 7.5 Hz, 1H), 5.83 (dt, J=15.6, 1.2 Hz, 1H), 3.73 (s, 3H), 2.55—2.35 (m, 2H), 2.30—2.00 (m, 2H), 2.14 (s, 3H), 1.80—1.55 (m, 2H), 1.55—1.35 (m, 1H), 0.91 (d, J=6.6 Hz, 3H).

A solution of the above-described ester (335 mg, 1.69 mmol) in MeOH (5 ml) was vigorously stirred under hydrogen atmosphere in the presence of palladium on carbon (10 wt%, 35 mg) for 1.5 h. The catalyst was removed by filtration. The filtrate was evaporated to dryness to give an ester **72** as a colorless oil (323 mg, 95%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.67 (s, 3H), 2.50—2.35 (m, 1H), 2.29 (t, J=7.2 Hz, 2H), 2.14 (s, 3H), 1.80—1.00 (m, 8H), 0.88 (d, J=6.2 Hz, 3H).

Methyl (5*R*)-7-Acetoxy-5-methylheptanoate (73) To a stirred solution of **72** (323 mg, 1.61 mmol) in CH_2Cl_2 (5 ml) was added *m*-chloroperbenzoic acid (1.19 g, 4.84 mmol) at room temperature under argon atmosphere. After being stirred for 2 d, the reaction mixture was diluted with hexane, and filtered. The filtrate was evaporated, and a stirred solution of the resulting residue in CH_2Cl_2 (5 ml) was treated with *m*-chloroperbenzoic acid (2.2 g, 9.68 mmol) at room temperature under argon atmosphere. After being stirred for additional 3 d, the reaction mixture was diluted with hexane, and filtered. The filtrate was evaporated to give acetate **73** (441 mg, 100%).^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.20—4.00 (m, 2H), 3.67 (s, 3H), 2.30 (t, J=7.2 Hz, 2H), 2.04 (s, 3H), 1.80—1.10 (m, 7H), 0.92 (d, J=6.6 Hz, 3H).

Methyl (5*R*)-7-Iodo-5-methylheptanoate (61) To a stirred solution of the acetate **73** (441 mg, 2.04 mmol) in MeOH (3 ml) was added potassium carbonate (280 mg, 2.04 mmol) at room temperature under argon atmosphere. The reaction was quenched with saturated aqueous NH_4Cl and the reaction mixture was extracted with EtOAc, washed with H_2O twice, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 3/2) to give an alcohol as a colorless oil (182 mg, 65% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.85—3.60 (m, 2H), 3.67 (s, 3H), 2.31 (t, J=6.8 Hz, 2H), 1.80—1.10 (m, 8H), 0.91 (d, J=6.6 Hz, 1H).

To a stirred solution of the above-described alcohol (180 mg, 1.03 mmol) and triethylamine (0.36 ml, 2.58 mmol) in CH_2Cl_2 (5 ml) was added methanesulfonyl chloride (0.096 ml, 1.24 mmol) at 0 °C under argon atmosphere. After being stirred at the same temperature for 30 min, the reaction was quenched with H_2O and the reaction mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to yield a methanesulfonate as a yellow oil. To a stirred solution of the above-described methanesulfonate in acetone (3 ml) was added sodium iodide (930 mg, 6.20 mmol) at room temperature under argon atmosphere, and stirring was continued at 55 °C for 2 h. The resulting yellow solution was diluted with EtOAc, washed with water, then brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to afford **61** as a yellow oil (279 mg, 95%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.68 (s, 3H), 3.30—3.10 (m, 2H), 2.31 (t, J=7.4 Hz, 2H), 1.90 (m, 1H), 1.50—1.00 (m, 2H), 0.89 (d, J=6.2 Hz, 3H).

Methyl (5*R*)-7-[(2*R*)-2-{(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]-5-methylheptanoate (64) Compound **64** was prepared from **59** using iodide **61** according to the same procedure as described for the preparation of **63** from **59** using iodide **60** as a pale yellow oil (51%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.00 (m, 4H), 5.68 (dd, J=15.0, 5.4 Hz, 1H), 5.41 (ddd, J=15.0, 8.7, 1.5 Hz, 1H), 4.43 (s, 2H), 4.35 (m, 1H), 4.05 (m, 1H), 3.66 (s, 3H), 3.58 (m, 1H), 3.38 (s, 3H), 2.80—2.60 (m, 3H), 2.45—2.10 (m, 5H), 1.70—1.00 (m, 8H), 0.90 (d, J=6.6 Hz, 3H), 0.84 (s, 9H), −0.11 (s, 3H), −0.21 (s, 3H).

(5*R*)-7-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}-5-oxopyrrolidin-1-yl)-5-methylheptanoic Acid (14) Compound **14** was prepared from **64** according to the same procedure as described for the preparation of **13** from **63** as a pale yellow oil (86%). IR (film) cm^{-1}: 3389, 2927, 1725, 1659, 1461, 1421, 1382, 1258, 1190, 1098, 1038, 974, 919, 792, 736, 703, 665. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.10 (m, 4H), 5.78 (dd, J=15.4, 5.6 Hz, 1H), 5.54 (dd, J=15.4, 8.4 Hz, 1H), 4.50—4.35 (m, 1H), 4.41 (s, 2H), 4.06 (m, 1H), 3.55 (m, 1H), 3.42 (s, 3H), 3.00—2.75 (m, 3H), 2.50—2.10 (m, 5H), 1.80—1.10 (m, 8H), 0.91 (d, J=5.8 Hz, 3H). MS (APCI) *m*/*z*: 416 $(M-H)^-$. HR-MS-FAB (*m*/*z*): 416.2433 (Calcd for $C_{24}H_{34}NO_5$: 416.2437).

3-Iodo-3-buten-1-yl Acetate (74) To a stirred solution of 3-hexyn-1-ol (1.40 g, 20.0 mmol) in pyridine (5 ml) was added acetic anhydride (2.30 ml, 24.0 mmol) at room temperature under argon atmosphere. After being stirred for 2 h, the reaction mixture was diluted with Et_2O, washed with 1 N HCl, H_2O, brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation (below 10 °C) to give an *O*-acetate.

To a stirred solution of sodium iodide in CH_3CN (20 ml) was added trimethylsilyl chloride (2.80 ml, 22.0 mmol) and H_2O (0.20 ml, 11.0 mmol) at room temperature under argon atmosphere. After being stirred for 5 min, the reaction mixture was treated with a solution of the above-described acetate in CH_3CN (2 ml). Stirring was continued for additional 1 h and the reaction mixture was diluted with Et_2O, washed with H_2O twice, brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 15/1—2/1) to give a vinyl iodide **74** as a colorless oil (2.24 g, 47% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.12 (q, J=1.0 Hz, 1H), 5.82 (m, 1H), 4.20 (t, J=6.2 Hz, 2H), 2.72 (tq, J=6.2, 1.0 Hz, 2H), 2.08 (s, 3H).

Methyl 7-Hydroxy-5-methyleneheptanoate (75) To a stirred suspension of zinc (0.98 g, 15 mmol) in THF (10 ml) were added dibromoethane (0.043 ml, 0.50 mmol) and trimethylsilyl chloride (0.063 ml, 0.50 mmol) at room temperature under argon atmosphere. After being stirred for 20 min, the reaction mixture was treated with a solution of methyl 4-iodobutanoate (2.28 g, 10.0 mmol) in THF (10 ml). Stirring was continued at 55 °C for additional 1 h. The resulting solution was cooled to room temperature.

To a stirred solution of **74** (2.24 g, 9.30 mmol) in DMF (20 ml) was added a solution of 4-ethoxy-4-oxobutylzinc iodide (0.5 M in THF, 20.0 ml, 10.0 mmol) and tetrakis(triphenylphosphine)palladium (580 mg, 0.50 mmol) at room temperature under argon atmosphere. After being stirred for 16 h, the reaction mixture was diluted with Et_2O, washed with H_2O twice, then brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 10/1) to give an olefin as a pale yellow oil (1.36 g, 68%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 4.85—4.80 (m, 2H), 4.18 (t, J=7.2 Hz, 2H), 3.67 (s, 3H), 2.42—2.25 (m, 4H), 2.09 (t, J=7.2 Hz, 2H), 2.04 (s, 3H), 1.89—1.71 (m, 2H).

To a stirred solution of the above-described olefin (1.36 g, 6.30 mmol) in anhydrous MeOH (15 ml) was added potassium carbonate (880 mg, 6.30 mmol) at room temperature under argon atmosphere. After being stirred for 17 h, the reaction mixture was diluted with Et_2O and washed with 1 N HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed by evaporation and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 4/1—1/1) to give an alcohol **75** as a colorless oil (980 mg, 90%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.91—4.85 (m, 2H), 3.72 (q, J=6.2 Hz, 2H), 3.68 (s, 3H), 2.33 (t, J=7.2 Hz, 2H), 2.29 (t, J=6.2 Hz, 2H), 2.08 (t, J=7.2 Hz, 2H), 1.79 (m, 2H), 1.44 (t, J=6.2 Hz, 1H).

Methyl 4-[1-(2-Iodoethyl)cyclopropyl]butanoate (62) To a stirred solution of the alcohol **75** (980 mg, 5.70 mmol) in CH_2Cl_2 (12 ml) were successively added a solution of diethylzinc (1.0 M in hexane, 11.5 ml, 11.5 mmol) and diiodomethane (1.85 ml, 23.0 mmol) at 0 °C under argon atmosphere. Stirring was continued for 1 h and the reaction mixture was poured into 1 N HCl, extracted with $CHCl_3$. washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation and the resulting residue was purified

by column chromatography on silica gel (hexane/EtOAc, 4/1—1/1) to give a cyclopropyl alcohol as a colorless oil (980 mg, 90%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.80—3.70 (m, 2H), 3.68 (s, 3H), 2.32 (t, J=7.0 Hz, 2H), 1.81—1.65 (m, 2H), 1.66 (t, J=7.0 Hz, 2H), 1.45—1.33 (br s, 1H), 1.30—1.20 (m, 2H), 0.35—0.25 (m, 4H).

To a solution of the above-described cyclopropyl alcohol (1.80 mg, 0.97 mmol) and imidazole (95 mg, 1.40 mmol) in benzene (5 ml) was added a solution of iodine (305 mg, 1.20 mmol) in benzene (5 ml) at room temperature under argon atmosphere. After being stirred for 30 min, the reaction was quenched with MeOH. The resulting precipitates were removed by filtration and washed with Et_2O. The filtrate was evaporated and the resulting precipitates were removed by filtration again. The filtrate was evaporated again and the resulting residue was purified by column chromatography on silica gel (hexane/EtOAc, 9/1) to afford an iodide **62** as a colorless oil (232 mg, 81%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.68 (s, 3H), 3.18 (t, J=8.0 Hz, 2H), 2.31 (t, J=7.0 Hz, 2H), 1.85 (t, J=8.0 Hz, 2H), 1.75—1.60 (m, 2H), 1.31—1.20 (m, 2H), 0.41—0.29 (m, 4H).

Methyl 4-(1-{2-[(2*R*)-2-{(1*E*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]ethyl}cyclopropyl)butanoate (65) Compound **65** was prepared from **59** using iodide **62** according to the same procedure as described for the preparation of **63** from **59** using iodide **60** as a pale yellow oil (69%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.06 (m, 4H), 5.69 (dd, J=15.0, 6.0 Hz, 1H), 5.42 (d, J=15.0, 8.0 Hz, 1H), 4.42 (s, 2H), 4.35 (m, 1H), 4.00 (m, 1H), 3.66 (s, 3H), 3.67 (m, 1H), 3.38 (s, 3H), 2.80—2.70 (m, 3H), 2.43—2.10 (m, 5H), 1.75—1.60 (m, 3H), 1.50—1.22 (m, 4H), 0.82 (s, 9H), 0.35—0.23 (m, 4H), −0.11 (s, 3H), −0.22 (s, 3H).

4-{1-[2-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)phenyl]but-1-enyl}-5-oxopyrrolidin-1-yl)ethyl]cyclopropyl}butanoic Acid (15) Compound **15** was prepared from **65** according to the same procedure as described for the preparation of **13** from **63** as a colorless oil (100%). IR (film) cm^{-1}: 2922, 1726, 1659, 1454, 1422, 1383, 1265, 1194, 1160, 1097, 1039, 975, 755. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33—7.13 (m, 4H), 5.81 (dd, J=15.0, 5.6 Hz, 1H), 5.61 (dd, J=15.0, 8.0 Hz, 1H), 4.46 (s, 2H), 4.42 (m, 1H), 4.08 (m, 1H), 3.54 (m, 1H), 3.43 (s, 3H), 2.98 (m, 1H), 2.90 (dd, J=13.8, 8.8 Hz, 1H), 2.47—2.12 (m, 5H), 1.79—1.52 (m, 4H), 1.36—1.10 (m, 3H), 0.37—0.22 (m, 4H). MS (APCI) m/z: 428 $(M-H)^-$. HR-MS-FAB (m/z): 428.2439 (Calcd for $C_{25}H_{34}NO_5$: 428.2437).

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