Discovery of Orally Available 8-Aza-5-thiaProstaglandin E_1 Analogs as Highly Selective EP4 Agonists

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Analogs 8-aza-16-aryl prostaglandin E_1 (PGE_1) and 8-aza-5-thia-16-arylPGE_1 were synthesized and evaluated with respect to their subtype receptor affinity and EP4 agonist activity for the purposes of identifying subtype-selective EP4 agonists that demonstrate oral efficacy. Using an inhibition assay of lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)-α production in rats, representative compounds were evaluated for their pharmacokinetic profiles and *in vivo* efficacy. Structure–activity relationships (SARs) were characterized and presented. Of the compounds tested, several demonstrated better oral exposure and/or *in vivo* efficacy compared with the previously reported analog 2a.

Key words prostaglandin; agonist; EP4-receptor; tumor necrosis factor-α

Prostanoids, which consist of prostaglandins (PGs) and thromboxanes (TXs), are derived from arachidonic acid *via* oxidative metabolism induced by cyclooxygenases. Once prostanoids are produced, they act on G-protein-coupled receptors in the tissues they were synthesized. Each of these receptors has been cloned, expressed, and characterized. Coleman *et al.* proposed that there are receptors specific for PGE, PGF, PGI, PGD, and TX, which were classified into EP, FP, IP, DP and TP receptors, respectively.[1)] They further classified the EP receptors into four subtypes (EP1, EP2, EP3 and EP4), all of which respond to PGE_2 in different ways. Characterization of these receptors at the molecular level has resulted in renewed interest in this field. As such, a number of ligands selective for each of these EP subtype receptors have been studied as potential therapeutics.

Stimulation of the EP4 receptor with PGE_2 leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) levels, which has been suggested to be coordinated with the cytoprotective effects of PGE_2, such as protection of organs and/or tissue from damage. Highly potent EP4 subtype-selective receptor agonists have been suggested to have therapeutic potential without side effects, such as uterine contractions, which are considered to be mediated by the EP3 subtype. Previously, we discovered 5-thiaPGE_1 **1** (Fig. 1), a highly potent EP4 subtype selective agonist, which suppresses the lipopolysaccharide (LPS)-induced production of tumor necrosis factor (TNF)-α following its intravenous (i.v.) infusion.[2)] However, **1** demonstrated a poor pharmacokinetic (PK) profile (*i.e.* bioavailability $<1\%$), which was estimated to be mainly due to its metabolic instability and/or low membrane permeability (*i.e.* Caco-2 permeability of **1**: $<10^{-7}$ cm/s). Thus, the development of a structurally novel and orally available EP4 subtype-selective agonist has been warranted to serve as an orally available drug candidate. Several research groups have been investigating γ-lactam PGE analogs for the purpose of improving their chemical and metabolic stability.[3—6)] In a previous report,[7)] we identified γ-lactam PGE analogs **2a** and **3a** (Fig. 1), as novel chemical leads for a class of chemically and metabolically stable EP4 receptor agonists, which have a ω-chain moiety 16-(3-methoxymethyl)phenyl, based on previously reported data on cyclopentane PGE analogs.[2,7)] To further optimize these compounds and potentially identify an orally available EP4 subtype selective agonist, we wanted to focus on chemically modifying the 16-phenyl moiety of **2a** and **3a**. Thus, an investigation on the optimal ω-chain moiety of the new γ-lactam scaffolds was conducted. Herein, we report on the discovery of more optimized EP4 receptor agonists, **3b**, **c** and **3k**, derived from the chemical leads **2a** and **3a**. The structure–activity relationships (SARs) of these novel analogs are presented.

Chemistry The synthesis of compounds **2a** and **3a** was reported in our previous paper.[7)] The synthesis of test compounds listed in Table 1 is outlined in Charts 1a—e and 2a, b. Compounds **2b**—**j**, **3b**, **3d**—**i** and **3j** were synthesized as described in Chart 1a. 1-*N*-Alkyl 5-hydroxymethylpyrrolidin-2-ones **4a**, **b**[7)] were oxidized with a sulfur trioxide-pyridine complex in dimethyl sulfoxide (DMSO) and the presence of diisopropylethylamine to yield the corresponding aldehydes **5a**, **b**, respectively. Horner–Emmons olefination of **5a**, **b** using an optional phosphonate of **10a**—**j** yielded **6a**—**c** and **7a**—**h**, respectively. A stereoselective reduction of these compounds with (*R*)-Me-CBS and borane-tetrahydrofuran (THF) complex yielded **8a**—**i** and **9a**—**h**, respectively. Alkaline hydrolysis of **8a**—**i** and **9a**—**h** resulted in **2b**—**j**, **3b**, **3d**—**i** and **3j**, respectively.

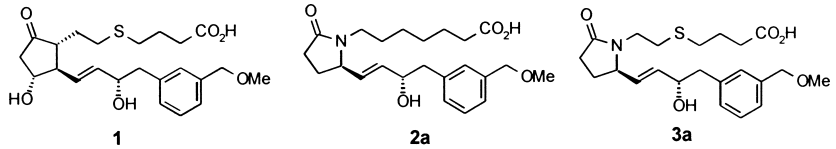

Fig. 1. The Reported Structures of Potent and Selective EP4 Agonists

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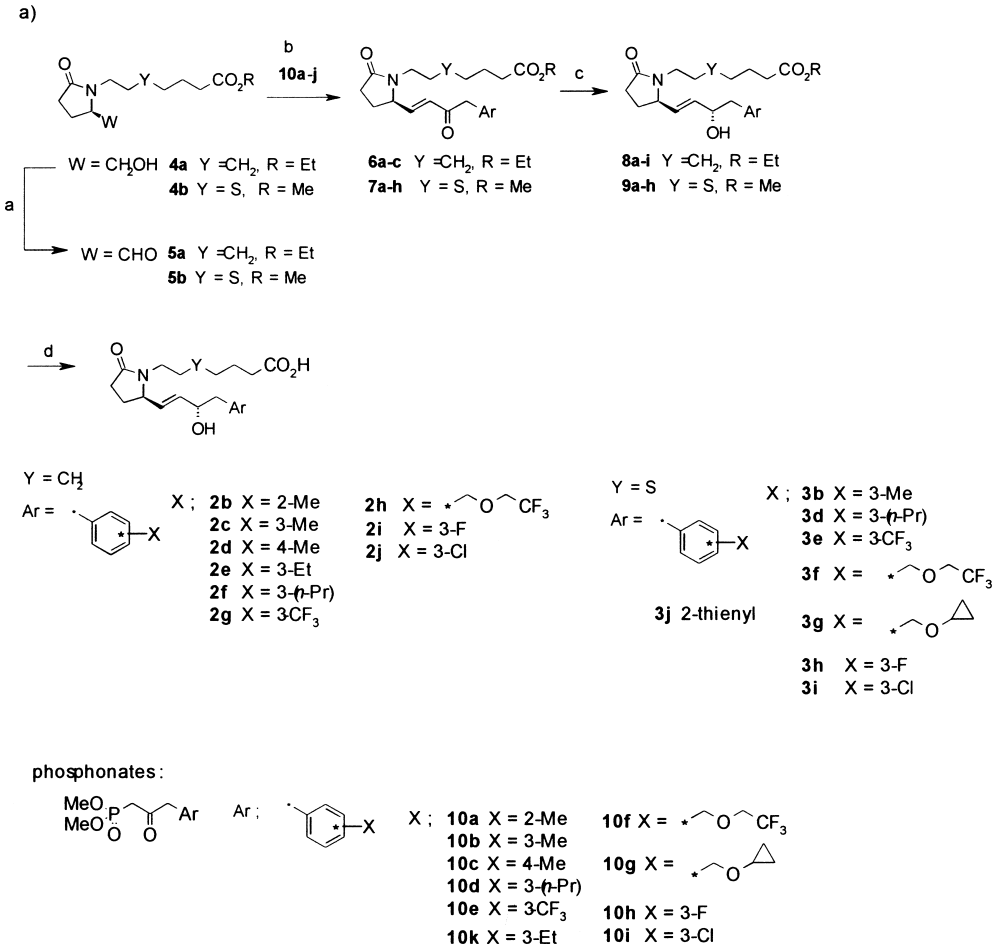
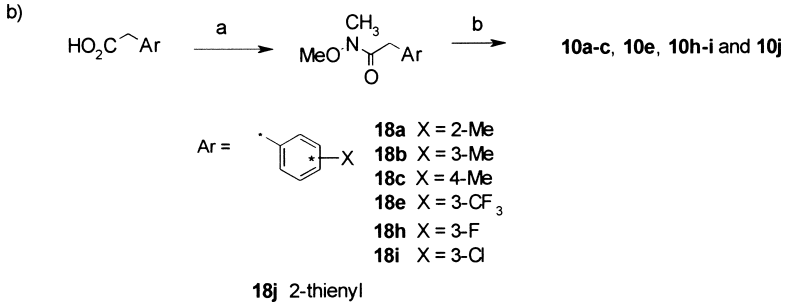


Reagents: a) SO_3-Py, *i*-Pr_2NEt, DMSO, AcOEt; b) **10a**—**j**, NaH, THF; c) (*R*)-Me-CBS, BH_3-THF, THF; and d) aq. NaOH, MeOH, DME.

Chart 1a. Synthesis of **2b**—**j**, **3b**, **3d**—**i** and **3j**



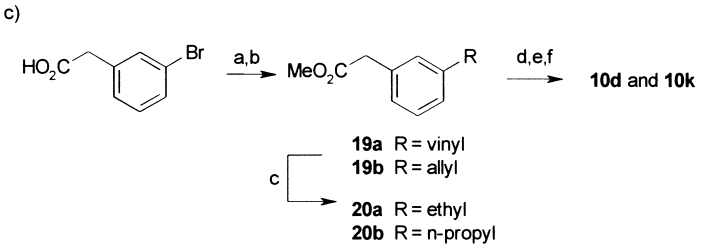
Reagents: a) *N*,*O*-dimethylhydroxylamine hydrochloride, EDC-HCl, Et_3N, CH_3CN; and b) dimethyl methylphosphonate, *n*-BuLi, toluene.

Chart 1b. Preparation of **10a**—**c**, **10e**, **10h**, **i** and **10j**

Phosphonates **10a**—**l** were prepared as outlined in Charts 1b—e. As shown in Chart 1b, commercially available phenylacetic acids were converted into corresponding Weinreb amides **18a**—**c**, **18e**, **18h**, **i** and **18j**, respectively, *via* peptide synthesis. They were then converted into phosphonates **10a**—**c**, **10e**, **10h**, **i** and **10j**, respectively, using a conventional procedure.

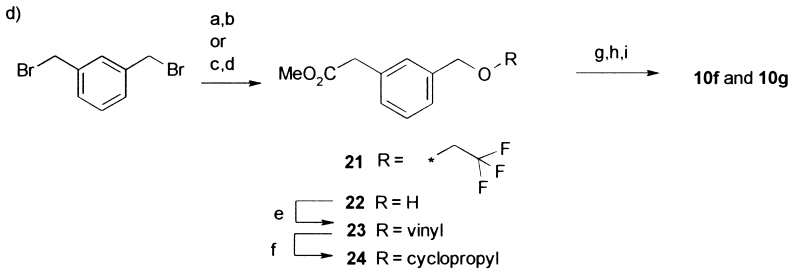
As shown in Chart 1c, phosphonates **10d** and **10k** were prepared from their corresponding phenylacetic acids using the same procedures described above. Esterification of a commercially available (*m*-bromophenyl)acetic acid followed by a treatment with alkenyl(tributyl)tin in the presence of *tetrakis*-triphenylphosphine palladium yielded methyl (*m*-alkenylphenyl)acetates **19a**, **b**. A catalytic hydrogenation of these compounds yielded methyl (*m*-alkylphenyl)acetates **20a**, **b**, respectively. Alkaline hydrolysis of **20a**, **b**, similar to that described above, resulted in **10d** and **10k**, respectively.

Phosphonates **10f**, **g** were prepared as shown in Chart 1d. Monosubstitution of the commercially available 1,3-bis(bromophenyl)benzene with sodium 2,2,2-trifluoroethoxide, followed by a palladium-catalyzed carbonyl insertion reaction in the presence of potassium carbonate and methanol yielded **21**, which was then converted into phosphonate **10f**, based on the same procedure described above. Monosubstitution of



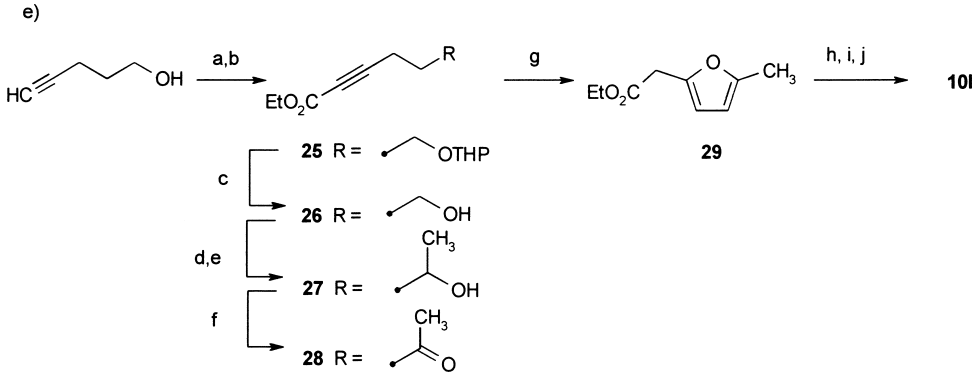
Reagents: a) MeI, K_2CO_3, DMF, 86%; b) alkenyl(tributyl)tin, $Pd(PPh_3)_4$, toluene; c) H_2, Pd–C, MeOH; d) aq. NaOH, MeOH; e) *N*,*O*-dimethylhydroxylamine hydrochloride, EDC-HCl, Et_3N, CH_3CN; and f) dimethyl methylphosphonate, *n*-BuLi, toluene.

Chart 1c. Preparation of **10d** and **k**



Reagents: a) CF_3CH_2OH, NaH, DMF, b) $PdCl_2(PPh_3)_2$, CO, K_2CO_3, MeOH, THF, 63% in 2 steps; c) AcOK, DMF; d) $PdCl_2(PPh_3)_2$, CO, K_2CO_3, MeOH, THF, 47% in 2 steps; e) $Pd(OAc)_2$, 1,10-phenanthroline, ethylvinyl ether, CH_2Cl_2, 70%; f) CH_2I_2, Et_2Zn, Et_2O, 57%; g) aq. NaOH, MeOH; h) *N*,*O*-dimethylhydroxylamine hydrochloride, EDC-HCl, Et_3N, CH_3CN; and i) dimethyl methylphosphonate, *n*-BuLi, toluene.

Chart 1d. Preparation of **10f** and **10g**



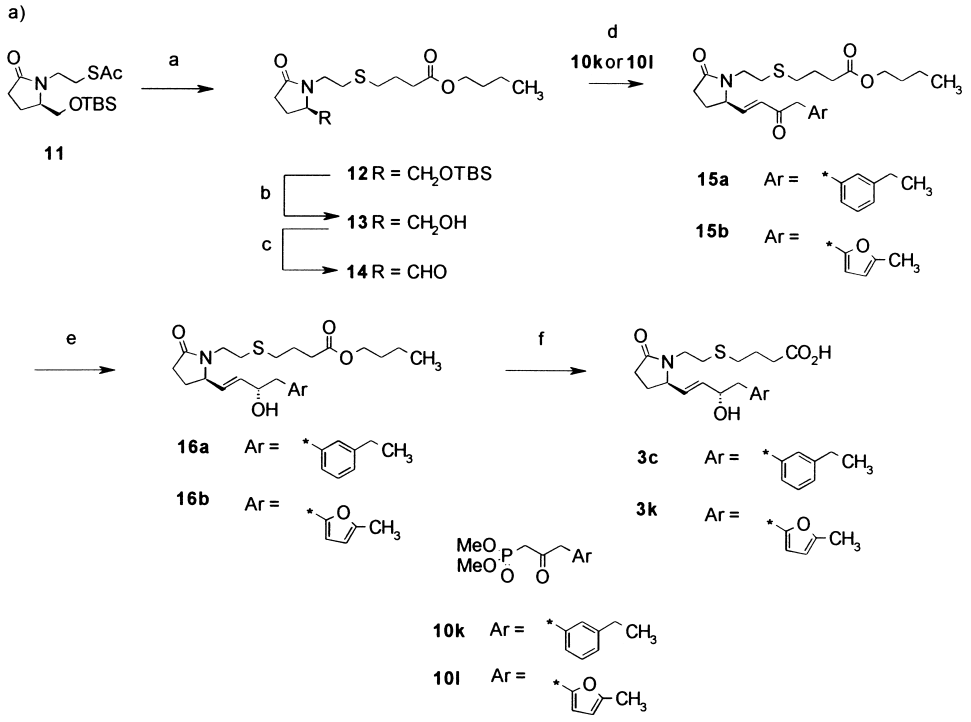
Reagents: a) 3,4-dihydro-2*H*-pyran, *p*-TsOH, CH_2Cl_2, 95%; b) *n*-BuLi, ethyl chloroformate, THF; c) *p*-TsOH, EtOH, 72%; d) $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2; e) MeMgBr, THF, 24%; f) $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 65%; g) NaH, DMF, 25%; h) aq NaOH, EtOH; i) *N*,*O*-dimethylhydroxylamine hydrochloride, EDC-HCl, Et_3N, CH_3CN; and j) dimethyl methylphosphonate, *n*-BuLi, toluene.

Chart 1e. Preparation of **10l**

1,3-bis(bromomethyl)benzene with potassium acetate, followed by a palladium-catalyzed carbonyl insertion reaction in the presence of potassium carbonate and methanol yielded **22**. A palladium-catalyzed vinylation of **22** with ethylvinyl ether in the presence of palladium diacetate and 1,10-phenanthroline yielded **23**.[8] Simmons–Smith reaction of **23** with diiodomethane and diethylzinc yeilded **24**. Based on the same procedure described above, **24** was converted into **10g**.

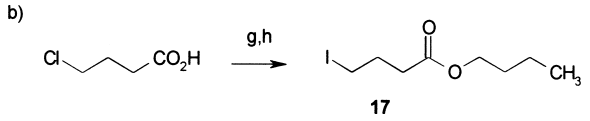
Phosphonate **10l** was prepared as shown in Chart 1e. *O*-Protection of the commercially available 4-butyn-1-ol as a tetrahydropyranyl ether, followed by ethoxycarbonylation with ethyl chloroformate in the presence of *n*-butyllithium yielded **25**. An acidic deprotection **25** yielded **26**. Swern oxidation of **26**, followed by methylation of the produced aldehyde with a methyl Grignard reagent yielded **27**, and a repeated Swern oxidation of **27** resulted in a methyl ketone **28**. Treatment of **28** with sodium hydride in *N*,*N*-dimethylformamide yielded (5-methyl)furan-2-yl acetic acid **29**,[9] which was then converted into **10l**, similarly as described above.

The synthesis of **3c** and **k** is described in Chart 2a. Alcoholysis followed by an *S*-alkylation of 1-*N*-alkyl 5-*tert*-butyldimethylsilyloxymethylpyrrolidin-2-one **11** with an iodide **17**, as described in Chart 2b, yielded **12**, and deprotection of **12** with tetra-butylammonium fluoride (TBAF) yielded **13**. Oxidation of **13** produced an aldehyde **14**, which was easier to extract with an organic solvent, as it is more hydrophobic than the above mentioned corresponding methyl and ethyl esters **5a**, **b**. A Horner–Emmons olefination of **14** with phosphonates **10k**, **l** yielded enones **15a**, **b**, respectively, and



Reagents: a) **17**, KO^{t}Bu, *n*-butanol, THF; b) TBAF, THF, 80% in 2 steps; c) SO_3-Py, *i*-Pr_2NEt, DMSO, AcOEt; d) **10k**, **l**, NaH, THF; e) (*R*)-Me-CBS, BH_3-THF, THF; and f) aq NaOH, MeOH, DME.

Chart 2a. Synthesis of **3c** and **k**



Reagents: g) $SOCl_2$, *n*-butanol, 100%; and h) NaI, CH_3CN, 100%.

Chart 2b. Preparation of **17**

stereoselective reduction of enones **15a**, **b** with (*R*)-Me-CBS and borane–THF complex resulted in the desired diastereoisomers **16a**, **b**, respectively. Alkaline hydrolysis of **16a**, **b** yielded carboxylic acids **3c** and **3k**, respectively.

Results and Discussion

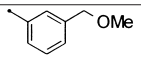
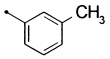
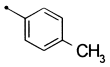
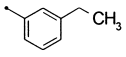
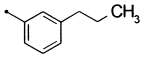
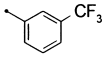
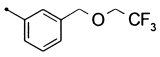
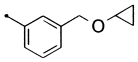
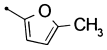
The compounds listed in Table 1 were evaluated for their binding affinity for mouse EP receptor subtypes. The agonist activities of these compounds on each of the EP4 receptor subtype were also evaluated.

Results are summarized in Table 1. Design and synthesis of 16-(2-methyl)phenyl, 16-(3-methyl)phenyl and 16-(4-methyl)phenyl analogs resulted in **2b**—**d**, respectively, with good to excellent EP4 subtype selectivity. Among the tested isomers, *meta*-isomer **2c** demonstrated the most potent receptor affinity and agonist activity for EP4 subtype, while 5-thia analog **3b** demonstrated equipotent receptor affinity and agonist activity with **2c**. *para*-Isomer **2d** demonstrated a 41-fold less potent EP4 affinity in comparison to **2c**, while *ortho*-isomer **2b** demonstrated a 94-fold less potent affinity. As a result, *ortho*- and *para*-substitution of the 16-phenyl moiety appears to be deleterious in EP4 receptor affinity. Based on these findings, more analogs, specifically **2e**, **f**, which possess a 16-(3-substituted)phenyl moiety, were synthesized and evaluated. Both analogs exhibited very potent affinity and subtype-selectivity for EP4 receptor, however there was a significant reduction in their agonist activity for their very potent receptor affinity. Meanwhile, 16-(3-alkyl)phenyl 5-thia analogs **3c**, **d** demonstrated very potent activity in both receptor affinity and agonist activity. A reduction in the agonist activity of **3c**, **d** was much lower compared with 5-methylene analogs **2e**, **f**, respectively. Furthermore, 5-thia analogs **3b**—**d** appeared to have more potent agonist activities than 5-methylene analogs **2c** and **2e**, **f**, respectively, while their EP4 receptor affinity did not differ between the two series of analogs. Similar SARs were also observed between **2g**, **h** and **3e**, **f**. Thus, an introduction of a 5-thia moiety appears to be effective in preventing a reduction in agonist activity due to presumed potential increase in the lipophilicity and/or bulkiness of the *meta*-substituent, as illustrated by the SARs of **2c**, **2e**—**h** and **3b**—**f**.

Interestingly, 5-thia-16-(3-fluoro)phenyl and 5-thia-16-(3-chloro)phenyl analogs **3h**, **i**, and 5-methylene analogs **2i**, **j** demonstrated completely opposite SARs, respectively, as shown in Table 1. The reason why the 5-thia-16-(3-fluoro)-phenyl analog **3h** exhibited reduced agonist activity relative to the corresponding 5-methylene analog **2i** is still not clear while the decreased agonist activity of 5-thia-16-(3-chloro)-phenyl analog **3i** relative to that of the corresponding 5-methylene analog **2j** seemed to be due to the decreased EP4 receptor affinity of **3i** relative to **2j**. Thus, 16-(3-fluoro)phenyl analogs **2i** and **3h** may have different SARs from 16-(3-alkyl)phenyl analogs.

The synthesis and evaluation of an 16-(3-cyclopropyl-oxymethyl)phenyl 5-thia analog **3g** resulted in the equipotency and subtype-selectivity that were similar to its structurally-related compounds **3a** and **3f**. The effects of replacing the terminal 16-phenyl moiety in the more optimized 5-thia

Table 1. Activity Profiles of 8-AzaPGE$_1$ Analogs

Compound	Y	Ar	Binding assay (K_i, nM) mEP1	mEP2	mEP3	mEP4	Functional assay (EC_{50}, nM) mEP4
2a	CH_2		$>10^4$	$>10^4$	$>10^4$	10	24
3a	S		$>10^4$	8500	$>10^4$	8.0	24
2b	CH_2		$>10^4$	$>10^4$	$>10^4$	170	NT
2c	CH_2		$>10^4$	$>10^4$	$>10^4$	1.8	44
3b	S		$>10^4$	$>10^4$	5800	1.8	29
2d	CH_2		$>10^4$	$>10^4$	1100	73	830
2e	CH_2		$>10^4$	$>10^4$	$>10^4$	0.8	2500
3c	S		$>10^4$	3100	560	0.7	9.7
2f	CH_2		$>10^4$	$>10^4$	$>10^4$	1.0	480
3d	S		$>10^4$	2000	500	0.7	48
2g	CH_2		$>10^4$	$>10^4$	$>10^4$	1.1	350
3e	S		$>10^4$	7500	920	1.0	27
2h	CH_2		$>10^4$	$>10^4$	$>10^4$	6.0	110
3f	S		$>10^4$	$>10^4$	$>10^4$	5.3	49
3g	S		$>10^4$	4400	$>10^4$	2.3	35
2i	CH_2		$>10^4$	$>10^4$	1500	2.0	79
3h	S		$>10^4$	$>10^4$	431	0.84	480
2j	CH_2		$>10^4$	$>10^4$	510	1.6	74
3i	S		$>10^4$	6900	$>10^4$	9.0	144
3j	S		$>10^4$	$>10^4$	550	3.6	11
3k	S		$>10^4$	$>10^4$	140	1.5	3.3

NT=not tested.

Table 2. Metabolic Stability in Liver Microsomes and Pharmacokinetic Profiles of the Representative Analogs

Compound	Stability in liver microsomes		Pharmacokinetic parameter				$c\log P$
	% remaining in RLM[a)]	% remaining in HLM[b)]	C_{max} (μg/ml)	$AUC_{p.o.}$ (μg/h/ml)	CL_{tot} (ml/h/kg)	BA (%)	
2a	NT	72[c)]	41	160	35	1.2[e)]	1.7
3b	100	93[d)]	117	343	32	11[f)]	2.2
3c	84	91[d)]	205	717	26	12[f)]	2.8
3k	85	93[d)]	2.7	11	33	2.8[g)]	1.4

a) RLM: rat liver microsomes. *b*) HLM: human liver microsomes. *c*) Liver microsomes, 1 mg/ml, incubation time, 60 min. *d*) Liver microsomes, 0.5 mg/ml, incubation time, 15 min. *e*) 1 mg/kg, i.v., 25 mg/kg, *p.o.* *f*) 1 mg/kg, i.v., 10 mg/kg, *p.o.* *g*) 0.75 mg/kg, i.v., 0.75 mg/kg, *p.o.* NT=not tested.

analogs with five-membered heterocyclic rings, such as thiophene and furan, on their activity profiles were also investigated. Replacement of the 16-phenyl moiety with 16-(thiophen-2-yl) and 16-(5-methylfuran-2-yl) moieties in these 5-thia analogs yielded **3j** and **k**, respectively. Both analogs demonstrated very potent EP4 receptor affinity with good agonist activity. In particular, **3k** exhibited the most potent agonist activity of all tested analogs.

Of the compounds tested, analogs **3b** and **3c** demonstrated improved PK profiles (C_{max} and *AUC*) and bioavailability compared with **2a** (Table 2). The membrane permeability of **3b**, **c** may, in part, improve their lipophilicity, and thereby their PK profiles and bioavailability. Conversely, the poor PK profile of **3k** may be a result of its relatively lower C_{max} and oral exposure (*AUC*), which may be due to its poor membrane permeability, as it has greater hydrophilicity. Furthermore, given that **3b**, **c** and **3k** were metabolically stable in rat liver microsomes (RLM) and human liver microsomes

Table 3. Agonist Activity of **2a**, **3b**, **c** and **3k** in Rat CHO Cells and Inhibition of LPS-Induced TNF-α Production in Rats

Compound	Functional assay	% inhibition of TNF-α production					
	rEP4 (EC_{50}, nM)	Dose (μg/kg, *p.o.*)	10	30	100	300	1000
2a	15					34	69
3b	5.7			29	64	81	
3c	3.0			18	63	82	
3k	0.69		25	51	79		

(HLM), these analogs may have been cleared through other metabolic pathways, such as b-oxidation, conjugation or excretion.Since our objective was to discover an orally available EP4 subtype selective agonist, we evaluated the biological properties of the developed compounds in an *in vivo* inhibition assay for LPS-induced TNF-α production in rats (Table 3). Additionally, prior to assessing the *in vivo* efficacy of EP4 subtype-selective agonists **2a**, **3b**, **c**, and **3k**, their pharmacokinetic profiles and intracellular cAMP production were evaluated in rat Chinese hamster ovary (CHO) cells expressing EP4-receptors. The results from these experiments are summarized in Table 3.

Lastly, **2a** demonstrated an ED_{50} at *ca.* 1000 μg/kg *per os* (*p.o.*), while **3b**, **c**, and **3k** demonstrated relatively higher *in vivo* potencies. Thus, an introduction of a sulfur atom in the 5-position, followed by chemical modification of the 16-phenyl moiety, resulted in enhanced *in vivo* efficacy. In particular, analog **3k** demonstrated a more potent *in vivo* efficacy (ED_{50}: 30 μg/kg, *p.o.*) compared with **2a** and **3b**, **c**. The significantly more potent functional activity of **3k** compared with other analogs was considered to be one of the plausible reasons of its higher *in vivo* efficacy.

Conclusion

In conclusion, a series of 8-aza-16-arylPGE$_1$ and 8-aza-5-thia-16-arylPGE$_1$ analogs were synthesized and investigated for their subtype receptor affinity and EP4 agonist activity. 16-(*meta*-Alkyl)phenyl analogs demonstrated excellent EP4 subtype-selectivity *via* binding assays. The discovery of **3b**, **c** and **3k**, which showed more improved bioavailability and/or *in vivo* efficacy compared with **2a**, was presented. Additionally, we found interesting SARs between two series of analogs, 5-methylene and 5-thia.

Based on our findings, the newly discovered subtype-selective EP4 agonists could have potential therapeutic benefits for the treatment of diseases, such as rheumatoid arthritis, inflammatory bowel disease, Crohn's disease and psoriasis, in which plasma TNF-α level are higher than normal.

Experimental

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 ($CDCl_3$) and deuterated methanol (CD_3OD) as the solvent. Fast atom bombardment (FAB-MS, 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), *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), sulfur trioxide/pyridine complex (SO_3-Py), 4-(dimethylamino)pyridine (DMAP), tetrabutylammonium fluoride (TBAF).

***N*-Methoxy-*N*-methyl-2-(2-methylphenyl)acetamide (18a)** To a stirred solution of *N*,*O*-dimethyl hydroxylamine hydrochloride (3.90 g, 40.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.64 g, 34.6 mmol) and triethylamine (5.6 ml, 40.0 mmol) in CH_3CN (15 ml) was added a solution of (2-methylphenyl)acetic acid (4.00 g, 26.6 mmol) in CH_3CN (17 ml) at room temperature under argon atmosphere. After being stirred for 1 h, the reaction was quenched with water. The reaction mixture was diluted with EtOAc, washed with 2 N HCl, water, then brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give a Weinreb amide **18a** as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24—7.07 (m, 4H), 3.77 (s, 2H), 3.61 (s, 3H), 3.21 (s, 3H), 2.31 (s, 3H).

3-(2-Methylphenyl)-2-oxopropanephosphonate (10a) To a stirred solution of dimethyl methylphosphonate (4.0 ml, 37.3 mmol) in toluene (80 ml) was added dropwise a solution of *n*-BuLi (1.57 M in hexane, 37.3 mmol) at −78 °C under argon atmosphere, and stirring was continued for 1 h at the same temperature. To the reaction mixture was added a solution of **18a** (26.6 mmol) in toluene (50 ml), and stirring was continued for additional 2 h at the same temperature. The reaction was quenched with acetic acid. The reaction mixture was allowed to warm up to room temperature with stirring. 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, 3/2—0/1) to give a phosphonate **10a** as a pale yellow oil (4.19 g, 61% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23—7.10 (m, 4H), 3.92 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.11 (d, J=22.8 Hz, 2H), 2.25 (s, 3H).

Ethyl 7-[(2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[2-methylphenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]heptanoate (8a) To a stirred solution of the alcohol **4a** (400 mg, 1.47 mmol) in EtOAc (3.5 ml) and diisopropylethylamine (1.5 ml, 8.84 mmol) was added a solution of SO_3-Py (704 mg, 4.42 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 **5a** as a pale yellow oil.

To a stirred solution of dimethyl 3-[(3-methylphenyl]-2-oxopropanephosphonate **10a** (264 mg, 1.03 mmol) in THF (10 ml) was added sodium hydride (63% in mineral oil, 35.0 mg, 0.884 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 **5a** in THF (1 ml) at 0 °C and stirring was continued for 2 h. The reaction mixture was quenched with acetic acid. The resulting solution was diluted with EtOAc, washed with water, then brine, and dried over $MgSO_4$. The solvent was removed by evaporation to give an enone **6a** as a pale yellow oil.

To a stirred solution of **6a** in THF (4.0 ml) was added a solution of (*R*)-2-methyl-CBS-oxazaborolidine (1.0 M in toluene, 0.184 ml, 0.184 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, 0.44 ml, 0.442 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. The solvent was removed by evaporation, and the resulting residue was purified by column chromatography on

silica gel ($CHCl_3$/MeOH, 70/1) to give an alcohol **8a** as a yellow viscous oil (183 mg, 62%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.05 (m, 4H), 5.75 (dd, J=15.3, 6.0 Hz, 1H), 5.50 (dd, J=15.3, 8.6 Hz, 1H), 4.40 (m, 1H), 4.11 (q, J=7.2 Hz, 2H), 4.03 (m, 1H), 3.45 (m, 1H), 2.86 (d, J=6.9 Hz, 2H), 2.71 (m, 1H), 2.44—2.10 (m, 6H), 2.34 (s, 3H), 1.90—1.18 (m, 12H).

7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(2-methylphenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}heptanoic Acid (2b) A solution of **8a** (130 mg, 0.324 mmol) in EtOH (0.3 ml), DME (0.1 ml) and 2 N NaOH (0.39 ml) was stirred at ambient temperature for 10 h. After neutralization with 2 N HCl (0.4 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 **2b** as a colorless oil (99 mg, 82%). IR (film): 2934, 2361, 1718, 1655, 1492, 1459, 1421, 1262, 1106, 1030, 974, 912, 746 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.28—7.00 (m, 4H), 5.76 (dd, J=15.2, 6.0 Hz, 1H), 5.49 (ddd, J=15.2, 8.4, 0.6 Hz, 1H), 4.42 (m, 1H), 4.04 (m, 1H), 3.46 (m, 1H), 2.87 (d, J=7.0 Hz, 2H), 2.72 (m, 1H), 2.50—2.04 (m, 6H), 2.34 (s, 3H), 1.85—1.10 (m, 9H); MS (APCI) m/z: 372 (M−H)$^-$; HR-MS-FAB (m/z): [M−H]$^-$ Calcd for $C_{22}H_{30}NO_4$, 372.2175; Found: 372.2180.

***N*-Methoxy-*N*-methyl-2-(3-methylphenyl)acetamide (18b)** Compound **18b** was prepared from (3-methylphenyl)acetic acid according to the same procedure as described of **18a** from (2-methylphenyl)acetic acid as a pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.21 (m, 1H), 7.11—7.04 (m, 3H), 3.73 (s, 2H), 3.61 (s, 3H), 3.19 (s, 3H), 2.33 (s, 3H).

3-(3-Methylphenyl)-2-oxopropanephosphonate (10b) Compound **10b** was prepared from **18b** according to the same procedure as described of **10a** from **18a** as a pale yellow oil (yield 74% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23 (m, 1H), 7.10—7.00 (m, 3H), 3.85 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.10 (d, J=22.5 Hz, 2H), 2.34 (s, 3H).

Ethyl 7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-methylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (8b) Compound **8b** was prepared from **5a** using **10b** instead of **10a** according to the same procedure as described of **8a** from **5a** as a pale yellow oil (yield 56% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25 (m, 1H), 7.07—6.98 (m, 3H), 5.73 (dd, J=15.3, 5.7 Hz, 1H), 5.50 (dd, J=15.3, 8.4 Hz, 1H), 4.40—4.38 (m, 1H), 4.11 (q, J=7.2 Hz, 2H), 4.15—3.99 (m, 2H), 3.52—3.42 (m, 1H), 2.81—2.68 (m, 3H), 2.34 (s, 3H), 2.34 (s, 3H), 2.40—2.10 (m, 6H), 1.80—1.20 (m, 8H), 1.25 (t, J=7.2 Hz, 3H).

7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-methylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (2c) Compound **2c** was prepared from **8b** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (yield 99%). IR (KBr): 3389, 2932, 2860, 1713, 1644, 1463, 1422, 1378, 1264, 1101, 1037, 974, 885, 784, 749, 702, 666 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.22—7.17 (m, 1H), 7.07—6.98 (m, 3H), 5.74 (dd, J=15.3, 5.7 Hz, 1H), 5.50 (ddd, J=15.3, 8.4, 1.2 Hz, 1H), 4.41 (m, 1H), 4.03 (m, 1H), 3.47 (m, 1H), 2.90—2.70 (m, 3H), 2.40—2.10 (m, 6H), 2.33 (s, 3H), 1.76—1.22 (m, 9H); MS (APCI) m/z: 372 (M−H)$^-$; HR-MS-FAB (m/z): [M−H]$^-$ Calcd for $C_{22}H_{30}NO_4$, 372.2175; Found: 372.2180.

Methyl 4-{(2-{(2*R*)-2-[(1*E*)-4-(3-Methylphenyl)-3-oxo-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio}butanoate (9a) Compound **9a** was prepared from **5b** using **10b** instead of **10a** according to the same procedure as described of **8a** from **5a** as a pale yellow oil (227 mg, 49% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.00 (m, 4H), 5.77 (dd, J=15.6, 6.0 Hz, 1H), 5.52 (ddd, J=15.6, 8.4, 0.9 Hz, 1H), 4.40 (m, 1H), 4.12 (m, 1H), 3.67 (s, 3H), 3.62 (m, 1H), 3.00—2.20 (m, 12H), 2.34 (s, 3H), 2.00—1.60 (m, 3H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-methylphenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3b) Compound **3b** was prepared from **9a** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (yield 99%). IR (KBr): 3362, 2922, 1726, 1660, 1487, 1447, 1419, 1361, 1232, 1161, 1100, 1036, 975, 909, 884, 855 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.21 (m, 1H), 7.07—6.98 (m, 3H), 5.78 (dd, J=15.3, 5.4 Hz, 1H), 5.52 (ddd, J=15.3, 8.7, 1.2 Hz, 1H), 4.43 (m, 1H), 4.11 (m, 1H), 3.62 (m, 1H), 2.95 (m, 1H), 2.83—2.20 (m, 11H), 2.34 (S, 3H), 2.00—1.80 (m, 2H), 1.70 (m, 1H); MS (APCI) m/z: 390 (M−H)$^-$; HR-MS-FAB (m/z): [M−H]$^-$ Calcd for $C_{21}H_{28}NO_4S$, 390.1739; Found: 390.1736.

***N*-Methoxy-*N*-methyl-2-(4-methylphenyl)acetamide (18c)** Compound **18c** was prepared from (4-methylphenyl)acetic acid according to the same procedure as described of **18a** from (2-methylphenyl)acetic acid as a pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.18 (d, J=8.2 Hz, 2H), 7.12 (d, J=8.2 Hz, 2H), 3.74 (s, 2H), 3.61 (s, 3H), 3.18 (s, 3H), 2.36 (s, 3H).

3-(4-Methylphenyl)-2-oxopropanephosphonate (10c) Compound **10c** was prepared from **18c** according to the same procedure as described of **10a** from **18a** as a pale yellow oil (yield 70% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.18—7.08 (m, 4H), 3.84 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 3.10 (d, J=22.5 Hz, 2H), 2.34 (s, 3H).

Ethyl 7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(4-methylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (8c) Compound **8c** was prepared from **5a** using **10c** instead of **10a** according to the same procedure as described of **8a** from **5a** as a pale yellow oil (yield 52% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.12 (d, J=8.2 Hz, 2H), 7.08 (d, J=8.2 Hz, 2H), 5.72 (dd, J=15.4, 6.0 Hz, 1H), 5.47 (dd, J=15.4, 8.5 Hz, 1H), 4.38 (m, 1H), 4.13 (q, J=7.1 Hz, 2H), 4.04 (m, 1H), 3.46 (m, 1H), 2.80 (d, J=6.9 Hz, 2H), 2.70 (m, 1H), 2.40—2.32 (m, 2H), 2.33 (s, 3H), 2.27 (t, J=7.4 Hz, 2H), 2.12 (m, 1H),1.71 (m, 1H), 1.67—1.58 (m, 2H), 1.49—1.20 (m, 6H), 1.23 (t, J=7.1 Hz, 3H).

7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(4-methylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (2d) Compound **2d** was prepared from **8b** according to the same procedure as described of **2b** from **8a** as a white powder (yield 83%). IR (KBr): 3223, 2935, 2862, 1723, 1660, 1513, 1459, 1422, 1378, 1328, 1264, 1241, 1190, 1151, 1111, 1034, 1007, 983, 912, 854, 811, 765, 726, 710, 570, 557, 485 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.12 (d, J=8.2 Hz, 2H), 7.07 (d, J=8.2 Hz, 2H), 5.73 (dd, J=15.38, 4.8 Hz, 1H), 5.47 (dd, J=15.4, 8.8 Hz, 1H), 4.38 (m, 1H), 4.03 (m, 1H), 3.46 (m, 1H), 2.81 (d, J=6.9 Hz, 2H), 2.72 (m, 1H), 2.40—2.27 (m, 4H), 2.34 (s, 3H), 2.21 (m, 1H), 1.72 (m, 1H), 1.67—1.58 (m, 2H), 1.50—1.18 (m, 6H); MS (APCI) m/z: 372 (M−H)$^-$; HR-MS-FAB (m/z): [M−H]$^-$ Calcd for $C_{22}H_{30}NO_4$, 372.2175; Found: 372.2160.

(3-Vinylphenyl)acetate (19a) To a stirred solution of (3-bromophenyl)-acetic acid (10.0 g, 46.5 mmol) and potassium carbonate (19.3 g, 140 mmol) in DMF (200 ml) was added methyl iodide (8.7 ml, 140 mmol) at room temperature under argon atmosphere. After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc (50 ml) and hexane (100 ml), 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, 5/1) to give an ester as a colorless oil (9.14 g, 86%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.49—7.37 (m, 2H), 7.21—7.17 (m, 2H), 3.74 (s, 3H), 3.60 (s, 2H).

To a stirred solution of above-described ester (5.0 g, 21.8 mmol) in toluene (40 ml) were added vinyltributyltin (6.7 ml, 22.9 mmol) and tetrakis(triphenylphosphine)palladium (504 mg, 0.44 mmol) at under argon atmosphere. After being stirred at 110 °C for 2 h, the reaction mixture was cooled to room temperature. The resulting mixture was filtered through a pad of Celite, and the filtrate was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 20/1—5/1) to afford **19a** as a colorless oil (3.17 g, 82%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35—7.24 (m, 3H), 7.18 (m, 1H), 6.70 (dd, J=17.6, 11.0 Hz, 1H), 5.76 (dd, J=17.6, 0.8 Hz, 1H), 5.25 (dd, J=11.0, 0.8 Hz, 1H), 3.72 (s, 3H), 3.63 (s, 2H).

(3-Ethylphenyl)acetate (20a) A solution of **19a** (1.0 g, 5.67 mmol) in MeOH (10 ml) was vigorously stirred under hydrogen atmosphere in the presence of palladium on carbon (100 mg) for 1 h. The catalyst was removed by filtration. The filtrate was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 4/1) to afford **20a** as a colorless oil (890 mg, 88%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24 (m, 1H), 7.14—7.07 (m, 3H), 3.71 (s, 3H), 3.61 (s, 2H), 2.65 (q, J=7.7 Hz, 2H), 1.24 (t, J=7.7 Hz, 3H).

3-(3-Ethylphenyl)-2-oxopropanephosphonate (10k) A solution of **20a** (890 mg, 5.0 mmol) in MeOH (4.0 ml) and 2 N NaOH (3.0 ml, 6.0 mmol) was stirred at room temperature for 1 h. After neutralization with 2 N HCl under cooling, the reaction mixture was extracted with EtOAc three times, and the organic layer was washed with brine, dried over $MgSO_4$. The organic solvent was removed by evaporation to afford a carboxylic acid as a white powder (855 mg, 100%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.23 (m, 1H), 7.16—7.08 (m, 3H), 3.62 (s, 2H), 2.64 (q, J=7.7 Hz, 2H), 1.23 (t, J=7.7 Hz, 3H).

Compound **10k** was prepared from above-described carboxylic acid according to the same procedure as described of **10a** from (2-methylphenyl)acetic acid as a colorless oil (yield 70% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25 (m, 1H), 7.12 (m, 1H), 7.06—7.00 (m, 2H), 3.86 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.12 (d, J=22.5 Hz, 2H), 2.74 (q, J=7.4 Hz, 2H), 1.23 (t, J=7.4 Hz, 3H).

Ethyl 7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-ethylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (8d) Compound **8d** was prepared from **5a** using **10k** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (yield 55% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.22 (m, 1H), 7.11 (m, 1H), 7.07—7.00 (m, 2H), 5.74 (dd, J=15.4, 5.8 Hz, 1H), 5.51 (ddd, J=15.4, 8.5, 1.1 Hz, 1H), 4.42 (m, 1H),

4.12 (q, *J*=7.1 Hz, 2H), 4.05 (m, 1H), 3.49 (m, 1H), 2.90—2.78 (m, 2H), 2.72 (m, 1H), 2.62 (q, *J*=7.7 Hz, 2H), 2.42—2.32 (m, 2H), 2.25 (t, *J*=7.4 Hz, 2H), 2.24 (m, 1H), 1.73 (m, 1H), 1.71—1.66 (m, 2H), 1.50—1.20 (m, 6H), 1.26 (t, *J*=7.7 Hz, 3H), 1.25 (t, *J*=7.1 Hz, 3H).

7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-ethylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (2e) Compound **2e** was prepared from **8d** according to the same procedure as described of **2b** from **8a** as a colorless oil(75 mg, yield 98%). IR (KBr): 2932, 1659, 1461, 1374, 1264, 1103, 1033, 974, 895, 796, 735, 704, 666, 578 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24 (t, *J*=7.3 Hz, 1H), 7.11—6.97 (m, 3H), 5.74 (dd, *J*=15.1, 5.9 Hz, 1H), 5.50 (ddd, *J*=15.1, 8.3, 1.0 Hz, 1H), 4.42 (m, 1H), 4.04 (m, 1H), 3.45 (m, 1H), 2.84—2.80 (m, 2H), 2.75 (m, 1H), 2.63 (q, *J*=7.8 Hz, 2H), 2.43—2.32 (m, 2H), 2.35 (t, *J*=7.3 Hz, 2H), 2.21 (m, 1H), 1.71 (m, 1H), 1.68—1.57 (m, 2H), 1.54—1.20 (m, 6H), 1.24 (t, *J*=7.8 Hz, 3H); MS (APCI) *m/z*: 386 $(M-H)^-$; HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{23}H_{34}NO_4$, 388.2488; Found: 388.2470.

3-(3-Propylphenyl)-2-oxopropanephosphonate (10d) Compound **10d** was prepared in the same procedure as described of **10k** from (3-bromophenyl)acetic acid as a colorless oil (2.96 g, yield 59% in 5 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29—7.01 (m, 4H), 3.86 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.10 (d, *J*=22.8 Hz, 2H), 2.57 (t, *J*=8.0 Hz, 2H), 1.76—1.50 (m, 2H), 0.93 (t, *J*=7.0 Hz, 3H).

Ethyl 7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-propylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (8e) Compound **8e** was prepared from **5a** using **10d** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (255 mg, yield 48% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.26—7.19 (m, 1H), 7.08—6.99 (m, 3H), 5.75 (dd, *J*=15.4, 5.6 Hz, 1H), 5.48 (ddd, *J*=15.4, 8.0, 1.2 Hz, 1H), 4.50—4.30 (m, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 4.13—4.00 (m, 1H), 3.55—3.40 (m, 1H), 2.90—2.10 (m, 8H), 1.80—1.20 (m, 13H), 1.25 (t, *J*=7.2 Hz, 3H), 0.94 (t, *J*=7.2 Hz, 3H).

7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-propylphenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (2f) Compound **2f** was prepared from **8e** according to the same procedure as described of **2b** from **8a** as a colorless oil (47 mg, yield 96%). IR (film): 3389, 2931, 2862, 1728, 1660, 1632, 1487, 1463, 1422, 1376, 1263, 1103, 1034, 973, 903 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25—7.19 (m, 1H), 7.08—7.00 (m, 3H), 5.75 (dd, *J*=15.3, 5.7 Hz, 1H), 5.51 (ddd, *J*=15.3, 8.4, 0.9 Hz, 1H), 4.41 (m, 1H), 4.05 (m, 1H), 3.48 (m, 1H), 2.90—2.70 (m, 3H), 2.57 (t, *J*=7.2 Hz, 2H), 2.50—2.10 (m, 5H), 1.80—1.20 (m, 11H), 0.94 (t, *J*=7.2 Hz, 3H); MS (APCI) *m/z*: 400 $(M-H)^-$; HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{24}H_{36}NO_4$, 402.2644; Found: 402.2633.

Methyl 4-{(2-{(2*R*)-2-[(1*E*)-4-(3-Propylphenyl)-3-oxo-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio}butanoate (9b) Compound **9b** was prepared from **5b** using **10d** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (155 mg, 49% in 3 steps). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.30—7.20 (m, 1H), 7.10—7.00 (m, 3H), 5.77 (dd, *J*=15.4, 5.6 Hz, 1H), 5.52 (dd, *J*=15.4, 9.4 Hz, 1H), 4.50—4.35 (m, 1H), 4.20—4.00 (m, 1H), 3.80—3.55 (m, 1H), 3.67 (s, 3H), 3.05—2.85 (m, 1H), 2.85—2.75 (m, 2H), 2.75—2.10 (m, 11H), 2.00—1.80 (m, 3H), 1.80—1.50 (m, 3H), 0.94 (t, *J*=6.8 Hz, 3H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-propylphenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3d) Compound **3d** was prepared from **9b** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (yield 99%). IR (film): 3387, 2927, 2870, 1726, 1660, 1445, 1419, 1384, 1235, 1103, 1032, 975, 909, 784, 705, 667 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.30—7.20 (m, 1H), 7.10—7.00 (m, 3H), 5.78 (dd, *J*=15.4, 5.4 Hz, 1H), 5.52 (dd, *J*=15.4, 8.4 Hz, 1H), 4.50—4.40 (m, 1H), 4.20—4.05 (m, 1H), 3.75—3.55 (m, 1H), 3.20—2.10 (m, 14H), 2.00—1.80 (m, 2H), 1.80—1.55 (m, 3H), 0.94 (t, *J*=7.2 Hz, 3H); MS (APCI) *m/z*: 418 $(M-H)^-$; HR-MS-FAB (*m/z*): $[M-H]^-$ Calcd for $C_{23}H_{32}NO_4S$, 418.2052; Found: 418.2049.

***N*-Methoxy-*N*-methyl-2-[3-(trifluoromethyl)phenyl]acetamide (18e)** Compound **18e** was prepared from 3-(trifluoromethyl)phenylacetic acid according to the same procedure as described of **18a** from (2-methylphenyl)acetic acid as a yellow oil.

3-[3-(Trifluoromethyl)phenyl]-2-oxopropanephosphonate (10e) Compound **10e** was prepared from **18e** according to the same procedure as described of **10a** from **18a** as a colorless oil (yield 57% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60—7.40 (m, 4H), 3.99 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.14 (d, *J*=22.8 Hz, 2H).

Ethyl 7-[(2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(trifluoromethyl)phenyl]-1-buten-1-yl]}-5-oxo-1-pyrrolidinyl]heptanoate (8f) Compound **8f** was prepared from **5a** using **10e** instead of **10a** according to the same procedure as described of **8a** from **5a** as a pale yellow oil (yield 52% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65—7.30 (m, 4H), 5.73 (dd, *J*=15.6, 5.6 Hz, 1H), 5.51 (ddd, *J*=15.6, 8.0, 1.2 Hz, 1H), 4.45 (m, 1H), 4.11 (q, *J*=7.4 Hz, 2H), 4.04 (m, 1H), 3.44 (m, 1H), 2.91 (d, *J*=6.6 Hz, 2H), 2.72 (m, 1H), 2.44—1.86 (m, 6H), 1.80—1.04 (m, 9H), 1.24 (t, *J*=7.4 Hz, 3H).

7-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(trifluoromethyl)phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl)heptanoate (2g) Compound **2g** was prepared from **8f** according to the same procedure as described of **2b** from **8a** as a white powder (yield 83%). IR (film): 2932, 1652, 1453, 1330, 1162, 1122, 1074, 1036, 975, 907, 800, 752, 705, 664 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.60—7.35 (m, 4H), 5.73 (dd, *J*=15.3, 5.9 Hz, 1H), 5.50 (ddd, *J*=15.3, 8.3, 0.9 Hz, 1H), 4.46 (m, 1H), 4.03 (m, 1H), 4.00—3.00 (m, 2H), 3.46 (m, 1H), 2.91 (d, *J*=6.3 Hz, 2H), 2.71 (m, 1H), 2.48—2.06 (m, 5H), 1.76—1.12 (m, 9H); MS (APCI) *m/z*: 426 $(M-H)^-$; HR-MS-FAB (*m/z*): $[M+H]^+$ Calcd for $C_{22}H_{29}F_3NO_4$, 428.2049; Found: 428.2057.

Methyl 4-{(2-{(2*R*)-2-[(1*E*)-4-(3-Trifluoromethylphenyl)-3-oxo-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio}butanoate (9c) Compound **9c** was prepared from **5b** using **10e** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (90 mg, 30% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.59—7.39 (m, 4H), 5.77 (dd, *J*=15.3, 5.4 Hz, 1H), 5.53 (dd, *J*=15.3, 8.6 Hz, 1H), 4.51—4.40 (m, 1H), 4.18—4.08 (m, 1H), 3.70—3.58 (m, 4H), 3.05—2.88 (m, 3H), 2.70—2.19 (m, 10H), 1.94—1.84 (m, 2H), 1.78—1.60 (m, 1H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-trifluoromethylphenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3e) Compound **3e** was prepared from **9c** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (67 mg, 100%). IR (film): 3388, 2925, 1724, 1660, 1450, 1421, 1330, 1163, 1122, 1074, 1035, 976, 800, 754, 705 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.59—7.38 (m, 4H), 5.82—5.71 (m, 1H), 5.60—5.41 (m, 1H), 4.57—4.40 (m, 1H), 4.20—4.06 (m, 1H), 3.70—3.59 (m, 1H), 3.15—2.81 (m, 3H), 2.80—2.01 (m, 10H), 1.99—1.80 (m, 2H), 1.79—1.60 (m, 1H); MS (APCI) *m/z*: 444 $(M-H)^-$; HR-MS-FAB (*m/z*): $[M-H]^-$ Calcd for $C_{21}H_{25}F_3NO_4S$, 444.1456; Found: 444.1476

{3-[(2,2,2-Trifluoroethoxy)methyl]phenyl}acetate (21) To a stirred suspension of sodium hydride (63% in mineral oil, 770 mg, 20.2 mmol) in THF (40 ml) was added trifluoroethanol (1.46 ml, 20.2 mmol) at 0 °C under argon atmosphere. After being stirred for 10 min, to this resulting solution was added a solution of 1,3-bis(bromomethyl)benzene (5.28 g, 20.2 mmol) in THF (10 ml). After being stirred for additional 4 h, the reaction mixture was poured into ice-cold aqueous NH_4Cl, extracted with EtOAc, washed with H_2O, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give an ether. To a stirred solution of the above-described ether in THF (30 ml) and MeOH (15 ml) were added potassium carbonate (5.0 g, 36.0 mmol) and bis(triphenylphosphine)palladium dichloride (280 mg, 0.40 mmol) under argon atmosphere, and the reaction vessel was replaced with CO gas repeatedly. After being stirred at room temperature for 3 h, the resulting mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 9/1) to afford **21** as a brown oil (3.28 g, 63%).

3-[3-(2,2,2-Trifluoroethoxymethyl)phenyl]-2-oxopropanephosphonate (10f) Compound **10f** was prepared from **21** according to the same procedure as described of **10d** from **20a** as a colorless oil (2.28 g, yield 52% in 3 steps). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.12 (m, 4H), 4.66 (s, 2H), 3.92 (s, 2H), 3.83 (q, *J*=8.8 Hz, 2H), 3.82 (s, 3H). 3.76 (s, 3H), 3.17 (d, *J*=22.8 Hz, 2H).

Ethyl 7-[(2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(2,2,2-trifluoroethoxymethyl)phenyl]-1-buten-1-yl]}-5-oxo-1-pyrrolidinyl]heptanoate (8g) Compound **8g** was prepared from **5a** using **10f** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (61 mg, yield 17% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40—7.10 (m, 4H), 5.74 (dd, *J*=15.4, 5.6 Hz, 1H), 5.51 (dd, *J*=15.4, 8.4 Hz, 1H), 4.66 (s, 2H), 4.50—4.35 (m, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 4.15—3.95 (m, 1H), 3.85 (q, *J*=8.8 Hz, 2H), 3.60—3.40 (m, 1H), 3.00—2.65 (m, 3H), 2.45—2.10 (m, 3H), 2.28 (t, *J*=7.4 Hz, 2H), 2.28 (t, *J*=7.4 Hz, 2H), 1.85—1.15 (m, 10H), 1.25 (t, *J*=7.2 Hz, 3H).

7-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(2,2,2-trifluoroethoxymethyl)-phenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl)heptanoate (2h) Compound **2h** was prepared from **8g** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (36 mg, 100%). IR (film): 3389, 2933, 2862, 1720, 1656, 1460, 1422, 1375, 1279, 1159, 1111, 1034, 968, 913, 793, 732, 705, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40—7.10 (m, 4H), 5.75 (dd, *J*=15.6, 5.6 Hz, 1H), 5.52 (dd, *J*=15.6, 8.4 Hz, 1H), 4.67 (s, 2H), 4.50—4.35 (m, 1H), 4.10—3.98 (m, 1H), 3.86 (q, *J*=8.8 Hz, 2H), 3.60—

3.35 (m, 1H), 3.00—1.80 (m, 6H), 2.33 (t, *J*=7.0 Hz, 2H), 1.80—1.55 (m, 3H), 1.55—1.10 (m, 6H); MS (APCI) *m/z*: 470 (M−H)$^-$; HR-MS-FAB (*m/z*): [M+H]$^+$ Calcd for $C_{24}H_{33}F_3NO_5$, 472.2311; Found: 472.2313.

Methyl 4-{(2-{(2*R*)-2-[(1*E*)-4-(3-(2,2,2-Trifluoroethoxymethyl) phenyl)-3-oxo-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio}butanoate (9d) Compound **9d** was prepared from **5b** using **10f** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (112 mg, 41% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38—7.15 (m, 4H), 5.77 (dd, *J*=15, 5.0 Hz, 1H), 5.53 (dd, *J*=15, 8.0 Hz, 1H), 4.68 (s, 2H), 4.48—4.39 (m, 1H), 4.16—4.07 (m, 1H), 3.84 (q, *J*=9.0 Hz, 2H), 3.68 (s, 3H), 3.68—3.56 (m, 1H), 3.03—2.92 (m, 1H), 2.92—2.80 (m, 2H), 2.69—2.48 (m, 4H), 2.48—2.33 (m, 4H), 2.33—2.16 (m, 1H), 1.95—1.85 (m, 3H), 1.79—1.63 (m, 1H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-(2,2,2-trifluoroethoxymethyl)-phenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3f) Compound **3d** was prepared from **9c** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (75 mg, 96%). IR (film): 3389, 2926, 1725, 1660, 1420, 1279, 1160, 969, 756, 705 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38—7.14 (m, 4H), 5.77 (dd, *J*=15, 6.0 Hz, 1H), 5.53 (dd, *J*=15, 8.8 Hz, 1H), 4.65 (s, 2H), 4.50—4.40 (m, 1H), 4.18—4.08 (m, 1H), 3.86 (q, *J*=9.0 Hz, 2H), 3.68—3.55 (m, 1H), 3.08—2.94 (m, 1H), 2.94—2.79 (m, 2H), 2.68—2.32 (m, 8H), 2.32—2.17 (m, 1H), 1.98—1.82 (m, 2H), 1.78—1.63 (m, 1H).; MS (APCI) *m/z*: 488 (M−H)$^-$; HR-MS-FAB (*m/z*): [M−H]$^-$ Calcd for $C_{23}H_{29}F_3NO_5S$, 488.1719; Found: 488.1719.

[3-(Hydroxymethyl)phenyl]acetate (22) To a stirred solution of 1,3-bis(bromomethyl)benzene (5.28 g, 20.0 mmol) in DMF (40 ml) was added potassium acetate (1.96 g, 20.0 mmol) at room temperature under argon atmosphere After being stirred at 60 °C for 3 h, the resulting solution was cooled to ambient temperature, and diluted with EtOAc/hexane, washed with water, dried over $MgSO_4$. The organic solvent was removed by evaporation to afford a monobromide as brown oil. To a stirred solution of above-described monobromide in MeOH (15 ml) and THF (30 ml) were added potassium carbonate (5.00 g, 36.2 mmol) and bis(triphenylphosphine)palladium dichloride (280 mg, 0.40 mmol) under argon atmosphere, and the reaction vessel was replaced with CO gas repeatedly. After being stirred at room temperature for 6 h, the resulting mixture was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 2/1—1/1) to afford **22** as a dark brown oil (1.68 g, 48% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.40—7.21 (m, 4H), 4.72 (d, *J*=6.0 Hz, 2H), 3.71 (s, 3H), 3.62 (s, 2H), 1.68 (t, *J*=6.0 Hz, 1H)

{3-[(Vinyloxy)methyl]phenyl}acetate (23) To a stirred solution of **22** (1.68 g, 9.30 mmol), ethyl vinyl ether (20 ml), 1,10-phenanthroline (85 mg, 0.47 mmol) in CH_2Cl_2 (5 ml) was added palladium acetate (106 mg, 0.47 mmol) at room temperature under argon atmosphere. After being stirred for 2 d, the resulting mixture was evaporated and purified by column chromatography on silica gel (hexane/EtOAc, 9/1) to afford **23** as a pale yellow oil (1.35 g, 70%). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.42—7.21 (m, 4H), 6.56 (dd, *J*=22.5, 9.0 Hz, 1H), 4.76 (s, 2H), 4.30 (dd, *J*=22.5, 3.0 Hz, 1H), 4.09 (dd, *J*=9.0, 3.0 Hz, 1H), 3.70 (s, 3H), 3.62 (s, 2H).

{3-[(Cyclopropyloxy)methyl]phenyl}acetate (24) To a stirred solution of **23** (1.35 g, 6.60 mmol) in diethyl ether (30 ml) were successively added a solution of diethylzinc (1.0 M in hexane, 13.0 ml, 13.0 mmol) and a solution of diiodomethane (3.75 g, 14 mmol) in diethyl ether (10 ml) at room temperature under argon atmosphere. Stirring was continued at 35 °C for 8 h and the reaction mixture was poured into 1 N HCl, extracted with diethyl ether, 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, 15/1—10/1) to give **24** as a colorless oil (830 mg, 57%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35—7.15 (m, 4H), 4.55 (s, 2H), 3.70 (s, 3H), 3.62 (s, 2H), 3.40—3.33 (m, 1H), 0.76—0.66 (m, 2H), 0.55—0.45 (m, 2H).

3-[3-(Cyclopropoxymethyl)phenyl]-2-oxopropanephosphonate (10g) Compound **10g** was prepared from **24** according to the same procedure as described of **10d** from **20a** as a colorless oil (668 mg, yield 57% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35—7.12 (m, 4H), 4.53 (s, 2H), 3.89 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.42—3.30 (m, 1H), 3.10 (d, *J*=22.8 Hz, 2H), 0.71—0.59 (m, 2H), 0.55—0.45 (m, 2H).

Methyl 4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-{3-[(2,2,2-trifluoroethoxy)-methyl]phenyl}-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoate (9f) Compound **9f** was prepared from **5b** using **10g** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (105 mg, yield 42% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.36—7.11 (m, 4H), 5.77 (dd, *J*=15.6, 6.0 Hz, 1H), 5.52 (d, *J*=15.6, 8.0 Hz, 1H), 4.55 (s, 2H), 4.48—4.38 (m, 1H), 4.15—4.08 (m, 1H), 3.68 (s, 3H), 3.67—3.57 (m, 1H), 3.40—3.32 (m, 1H), 3.02—2.92 (m, 1H), 2.92—2.78 (m, 2H), 2.69—2.48 (m, 4H), 2.48—2.33 (m, 4H), 2.32—2.17 (m, 1H), 1.95—1.85 (m, 3H), 1.78—1.63 (m, 1H), 0.69—0.62 (m, 2H), 0.55—0.47 (m, 2H).

4-{[2-((2*R*)-2-{(1*E*,3*S*)-3-Hydroxy-4-[3-(cyclopropoxymethyl)phenyl]-but-1-enyl}-5-oxopyrrolidin-1-yl)ethyl]sulfanyl}butanoic Acid (3g) Compound **3g** was prepared from **9f** according to the same procedure as described of **2b** from **8a** as a colorless viscous oil (73 mg, 100%). IR (film): 3389, 2924, 1726, 1660, 1419, 1345, 1210, 1122, 1037, 975, 791, 703 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37—7.11 (m, 4H), 5.80 (dd, *J*=15, 5 Hz, 1H), 5.55 (dd, *J*=15, 8.0 Hz, 1H), 4.56 (s, 2H), 4.50—4.40 (m, 1H), 4.17—4.08 (m, 1H), 3.63—3.51 (m, 1H), 3.42—3.36 (m, 1H), 3.11—3.00 (m, 1H), 2.89 (dd, *J*=14, 6.0 Hz, 1H), 2.80 (dd, *J*=14, 8.0 Hz, 1H), 2.72—2.32 (m, 8H), 2.31—2.17 (m, 1H), 1.98—1.83 (m, 2H), 1.79—1.65 (m, 1H), 0.71—0.49 (m, 4H); MS (APCI) *m/z*: 446 (M−H)$^-$; HR-MS-FAB (*m/z*): [M+H]$^+$ Calcd for $C_{24}H_{34}NO_5S$, 448.2158; Found: 448.2143.

***N*-Methoxy-*N*-methyl-2-(3-fluorophenyl]acetamide (18h)** Compound **18h** was prepared from (3-fluorophenyl)acetic acid according to the same procedure as described of **18a** from (2-methylphenyl)acetic acid as a pale yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.28 (m, 1H), 7.08—6.91 (m, 3H), 3.76 (s, 2H), 3.63 (s, 3H), 3.20 (s, 3H).

3-(3-Fluorophenyl)-2-oxopropanephosphonate (10h) Compound **10h** was prepared from **18h** according to the same procedure as described of **10a** from **18a** as a colorless oil (yield 78% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30 (m, 1H), 7.01—6.92 (m, 3H), 3.91 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.12 (d, *J*=22.8 Hz, 2H).

Ethyl 7-[(2*R*)-2-(1*E*,3*S*)-3-Hydroxy-4-(3-fluorophenyl]-1-buten-1-yl]}-5-oxo-1-pyrrolidinyl]heptanoate (8h) Compound **8h** was prepared from **5a** using **10h** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (225 mg, yield 53% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32—7.22 (m, 1H), 6.99—6.91 (m, 3H), 5.72 (dd, *J*=15.3, 5.7 Hz, 1H), 5.51 (ddd, *J*=15.3, 8.7, 1.2 Hz, 1H), 4.46—4.34 (m, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 4.06—3.99 (m, 1H), 3.51—3.41 (m, 1H), 2.85 (d, *J*=6.6 Hz, 2H), 2.75—2.65 (m, 1H), 2.40—2.10 (m, 5H), 1.70—1.20 (m, 7H), 1.25 (t, *J*=7.2 Hz, 3H).

7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-fluorophenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (2i) Compound **2i** was prepared from **8h** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (50 mg, 87%). IR (KBr): 3383, 2934, 2862, 1714, 1659, 1588, 1488, 1448, 1422, 1375, 1249, 1141, 1102, 1035, 975, 942, 888, 786, 754, 692, 666 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.32—7.23 (m, 1H), 6.99—6.90 (m, 3H), 5.72 (dd, *J*=15.3, 6.0 Hz, 1H), 5.50 (ddd, *J*=15.3, 8.4, 1.2 Hz, 1H), 4.42 (m, 1H), 4.03 (m, 1H), 3.46 (m, 1H), 2.85 (d, *J*=6.0 Hz, 2H), 2.70 (m, 1H), 2.40—2.10 (m, 6H), 1.75—1.20 (m, 9H).; MS (APCI) *m/z*: 376 (M−H)$^-$; HR-MS-FAB (*m/z*): [M−H]$^-$ Calcd for $C_{21}H_{27}FNO_4$, 376.1924; Found: 376.1933.

Methyl 4-{(2-{(2*R*)-2-[(1*E*)-4-(3-Fluorophenyl)-3-oxo-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio}butanoate (9f) Compound **9f** was prepared from **5b** using **10h** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (77 mg, 47% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29 (m, 1H), 7.03—6.92 (m, 3H), 5.76 (dd, *J*=15.4, 5.5 Hz, 1H), 5.51 (dd, *J*=15.4, 8.5 Hz, 1H), 4.42 (m, 1H), 4.15 (m, 1H), 3.64 (s, 3H), 3.61 (m, 1H), 2.96 (m, 1H), 2.84 (d, *J*=6.6 Hz, 2H), 2.70—2.52 (m, 4H), 2.47—2.34 (m, 4H), 2.23 (m, 1H), 1.96—1.84 (m, 2H), 1.72 (m, 1H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-fluorophenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3h) Compound **3h** was prepared from **9f** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (56 mg, 92%). IR (film): 3393, 2925, 1725, 1659, 1587, 1488, 1448, 1420, 1248, 1141, 1034, 976, 942, 886, 787, 753, 693 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27 (m, 1H), 7.00—6.89 (m, 3H), 5.75 (dd, *J*=15.4, 5.5 Hz, 1H), 5.50 (dd, *J*=15.4, 8.5 Hz, 1H), 4.42 (m, 1H), 4.11 (m, 1H), 3.62 (m, 1H), 2.92 (m, 1H), 2.84 (d, *J*=6.9 Hz, 2H), 2.67—2.51 (m, 4H), 2.50—2.41 (m, 2H), 2.38 (t, *J*=7.1 Hz, 2H), 2.22 (m, 1H), 1.94—1.83 (m, 2H), 1.66 (m, 1H); MS (APCI) *m/z*: 394 (M−H)$^-$; HR-MS-FAB (*m/z*): [M−H]$^-$ Calcd for $C_{20}H_{25}FNO_4S$, 394.1488; Found: 394.1495.

***N*-Methoxy-*N*-methyl-2-(3-chlorophenyl]acetamide (18i)** Compound **18i** was prepared from (3-chlorophenyl)acetic acid according to the same procedure as described of **18a** from (2-methylphenyl)acetic acid as a pale yellow oil.

3-(3-Chlorophenyl)-2-oxopropanephosphonate (10i) Compound **10i** was prepared from **18i** according to the same procedure as described of **10a** from **18a** as a colorless oil (yield 83% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.11 (m, 4H), 3.89 (s, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.12 (d, *J*=22.8 Hz, 2H).

Ethyl 7-[(2*R*)-2-(1*E*,3*S*)-3-Hydroxy-4-(3-chlorophenyl]-1-buten-1-yl}-5-oxo-1-pyrrolidinyl]heptanoate (8i) Compound **8i** was prepared from **5a** using **10i** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (56 mg, yield 18% in 3 steps). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.40—7.20 (m, 3H), 7.20—7.05 (m, 1H), 5.71 (dd, J=15.4, 5.8 Hz, 1H), 5.49 (dd, J=15.4, 8.4 Hz, 1H), 4.50—4.30 (m, 1H), 4.12 (q, J=7.2 Hz, 2H), 4.15—3.95 (m, 1H), 3.60—3.40 (m, 1H), 2.83 (d, J=6.0 Hz, 2H), 2.83—2.63 (m, 1H), 2.42—2.05 (m, 5H), 1.90—1.10 (m, 10H), 1.25 (t, J=7.2 Hz, 3H).

7-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-chlorophenyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}heptanoate (2j) Compound **2i** was prepared from **8i** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (35 mg, 87%). IR (film): 3377, 2932, 2860, 1721, 1658, 1422, 1263, 1081, 1034, 975, 910, 784, 732, 704, 685 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.35—7.15 (m, 3H), 7.15—7.00 (m, 1H), 5.72 (dd, J=15.8, 5.8 Hz, 1H), 5.48 (dd, J=15.8, 8.2 Hz, 1H), 4.42 (q, J=6.6 Hz, 1H), 4.10—3.98 (m, 1H), 3.60—3.40 (m, 1H), 2.83 (d, J=6.6 Hz, 2H), 3.00—2.10 (m, 4H), 2.34 (t, J=7.2 Hz, 2H), 1.80—1.55 (m, 3H), 1.55—1.10 (m, 6H); MS (APCI) m/z: 394 (M+2−H)$^-$, 392 (M−H)$^-$; HR-MS-FAB (m/z): [M+H]$^+$ Calcd for $C_{21}H_{29}ClNO_4$, 394.1785; Found: 394.1793.

Methyl 4-{(2-{(2*R*)-2-[(1*E*)-4-(3-Chlorophenyl)-3-oxo-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio}butanoate (9g) Compound **9g** was prepared from **5b** using **10i** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (137 mg, 44% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.30—7.20 (m, 3H), 7.20—7.05 (m, 1H), 5.75 (dd, J=15.4, 5.6 Hz, 1H), 5.50 (dd, J=15.4, 8.4 Hz, 1H), 4.50—4.35 (m, 1H), 4.20—4.10 (m, 1H), 3.67 (s, 3H), 3.65—3.55 (m, 1H), 3.05—2.85 (m, 1H), 2.83 (d, J=6.6 Hz, 2H), 2.80—2.10 (m, 9H), 2.05—1.95 (m, 1H), 1.95—1.80 (m, 2H), 1.80—1.60 (m, 1H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-chlorophenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3i) Compound **3i** was prepared from **9g** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (90 mg, 100%). IR (film): 3375, 2925, 1722, 1659, 1420, 1232, 1080, 1033, 976, 784, 755, 704 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.30—7.20 (m, 3H), 7.20—7.05 (m, 1H), 5.75 (dd, J=15.4, 5.4 Hz, 1H), 5.49 (dd, J=15.4, 8.6 Hz, 1H), 4.50—4.35 (m, 1H), 4.20—4.05 (m, 1H), 3.75—3.55 (m, 1H), 3.10—2.85 (m, 1H), 2.85 (d, J=6.6 Hz, 2H), 2.80—2.10 (m, 9H), 2.00—1.80 (m, 2H), 1.80—1.60 (m, 1H); MS (APCI) m/z: 412 (M+2−H)$^-$, 410 (M−H)$^-$.

***N*-Methoxy-*N*-methyl-2-(2-thienyl)acetamide (18j)** Compound **18j** was prepared from 2-(thiophen-2-yl) acetic acid according to the same procedure as described of **18a** from (2-methylphenyl)acetic acid as a yellow oil.

3-(3-Fluorophenyl)-2-oxopropanephosphonate (10j) Compound **10j** was prepared from **18j** according to the same procedure as described of **10a** from **18a** as a colorless oil (yield 68% in 2 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.27 (m, 1H), 7.03—6.92 (m, 2H), 4.10 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.16 (d, J=22.8 Hz, 2H).

Methyl 4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-thien-2-ylbut-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoate (9h) Compound **9h** was prepared from **5b** using **10j** instead of **10a** according to the same procedure as described of **8a** from **5a** as a yellow oil (275 mg, yield 50% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.36—7.20 (m, 1H), 7.05—6.90 (m, 2H), 6.71 (dd, J=15.6, 8.0 Hz, 1H), 6.28 (d, J=15.6, 1H), 4.35—4.23 (m, 1H), 4.05 (s, 2H), 3.91—3.60 (m, 4H), 3.03—2.93 (m, 1H), 2.82—2.27 (m, 7H), 2.00—1.78 (m, 3H), 1.62—1.50 (m, 2H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-thien-2-ylbut-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic acid (3j) Compound **3j** was prepared from **9h** according to the same procedure as described of **2b** from **8a** as a colorless viscous oil (67 mg, 100%). IR (film): 3388, 2924, 1721, 1657, 1420, 1243, 1042, 976, 910, 850, 732 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.19 (d, J=5.1 Hz, 1H), 6.95 (dd, J=5.1, 3.3 Hz, 1H), 6.86 (d, J=3.3 Hz, 1H), 5.75 (dd, J=15.0, 5.4 Hz, 1H), 5.55 (dd, J=15.0, 8.6 Hz, 1H), 4.48—4.39 (m, 1H), 4.19—4.06 (m, 1H), 3.70—3.59 (m, 1H), 3.42—2.75 (m, 4H), 2.70—2.18 (m, 10H), 1.99—1.84 (m, 2H), 1.79—1.62 (m, 1H); MS (APCI) m/z: 382 (M−H)$^-$; HR-MS-FAB (m/z): [M−H]$^-$ Calcd for $C_{18}H_{24}NO_4S_2$, 382.1147; Found: 382.1164.

6-(Tetrahydro-2*H*-pyran-2-yloxy)-2-hexynoate (25) To a stirred solution of 4-butyn-1-ol (4.21 g, 50.0 mmol) in CH_2Cl_2 (50 ml) was added 3,4-dihydro-2*H*-pyran (5.02 ml, 55.0 mmol) and *p*-toluenesulfonic acid monohydrate (475 mg, 2.50 mmol) at room temperature under argon atmosphere. After being stirred for 10 min, the reaction was treated with triethylamine. 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 ether as a pale yellow oil (8.01 g, 95%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.60 (m, 1H), 3.85 (m, 2H), 3.50 (m, 2H), 2.31 (m, 2H), 1.95 (t, J=2.7 Hz, 1H), 1.90—1.50 (m, 8H).

To a stirred solution of **25** (8.01 g, 47.6 mmol) in THF (100 ml) was slowly added *n*-butyllithium (1.56 M in hexane, 33.6 ml, 52.4 mmol) at −70 °C under argon atmosphere and stirring was continued for 1 h at the same temperature. To the reaction mixture was slowly added ethyl chloroformate (13.7 ml, 143 mmol). After being stirred for additional 3 h at room temperature, the reaction mixture was poured into ice-cold aqueous NH_4Cl, extracted with EtOAc, 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, 4/1) to give **25** as a colorless oil (11.4 g, 100%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.59 (m, 1H), 4.21 (q, J=6.9 Hz, 2H), 3.90—3.70 (m, 12H), 3.55—3.41 (m, 2H), 2.47 (t, J=7.0 Hz, 2H), 1.93—1.50 (m, 8H), 1.30 (t, J=7.5 Hz, 3H).

6-Hydroxy-2-hexynoate (26) A mixture of **25** (11.4 g, 47.4 mmol) and *p*-toluenesulfonic acid monohydrate (900 mg, 4.74 mmol) in EtOH (50 ml) was stirred at room temperature for 3 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) to yield **26** as a colorless oil (5.30 g, 72%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.21 (q, J=7.2 Hz, 2H), 3.76 (t, J=6.0 Hz, 2H), 2.48 (t, J=6.9 Hz, 2H), 1.84 (m, 2H), 1.31 (t, J=6.9 Hz, 3H).

6-Hydroxy-2-heptynoate (27) To a stirred solution of oxalyl chloride (4.15 ml, 47.6 mmol) in CH_2Cl_2 (40 ml) was slowly added a solution of DMSO (4.34 ml, 61.2 mmol) in CH_2Cl_2 (20 ml) at −70 °C in 10 min. The resulting solution was stirred for an additional 15 min at that temperature. To the reaction mixture was added a solution of **26** (5.30 g, 34.0 mmol) in CH_2Cl_2 (10 ml)in, and the resulting suspension was allowed to warm up to −35 °C in 30 min. After being stirred for an additional 10 min, the reaction mixture was treated with *N*,*N*-diisopropylethylamine (16.6 ml, 95.2 mmol) and the resulting suspension was allowed to warm up to −5 °C in 30 min. The reaction was quenched with water and then poured into ice-cold 0.5 N HCl. The mixture was extracted with EtOAc and the organic layer was washed with 1 N HCl, water and brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give an aldehyde as a pale yellow oil.

To a stirred solution of an above-described aldehyde in THF (70 ml) was added a solution of methylmagnesium bromide (0.93 M in THF, 40.2 ml, 37.4 mmol) at 0 °C under argon atmosphere. After being stirred for 15 min, 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 and the resulting mixture was purified by column chromatography on silica gel (hexane/EtOAc, 4/1) to yield **27** as a colorless oil(1.41 g, 24%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.21 (q, J=7.2 Hz, 2H), 3.90 (m, 1H), 2.48 (t, J=7.5 Hz, 2H), 1.69 (m, 2H), 1.55 (br s, 1H), 1.40—1.28 (m, 8H).

6-Oxo-2-heptynoate (28) To a stirred solution of oxalyl chloride (1.01 ml, 11.6 mmol) in CH_2Cl_2 (10 ml) was slowly added a solution of DMSO (1.06 ml, 14.9 mmol) in CH_2Cl_2 (5 ml) at −70 °C in 10 min. The resulting solution was stirred for an additional 15 min at that temperature. To the reaction mixture was added a solution of **27** (1.41 g, 8.29 mmol), and the resulting suspension was allowed to warm up to −35 °C in 30 min. After being stirred for an additional 10 min, the reaction mixture was treated with *N*,*N*-diisopropylethylamine (4.04 ml, 23.3 mmol) and the resulting suspension was allowed to warm up to −5 °C in 30 min. The reaction was quenched with water and then poured into ice-cold 0.5 N HCl. The mixture was extracted with EtOAc and the organic layer was washed with 1 N HCl, water and brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give a methyl ketone **28** as a pale brown oil (794 mg, 57%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.21 (q, J=7.2 Hz, 2H), 2.76 (t, J=6.9 Hz, 2H), 2.59 (t, J=6.9 Hz, 2H), 2.19 (s, 3H), 1.30 (t, J=7.2 Hz, 3H).

(5-Methyl-2-furyl)acetate (29) To a stirred solution of **28** (637 mg, 3.79 mmol) in DMF (75 ml) was added sodium hydride (62% in mineral oil, 161 mg, 4.17 mmol) at room temperature under argon atmosphere, and then stirring was continued at 90 °C for 3 h. After being cooled to room temperature, the reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with MTBE, 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 an ester **29** as a pale yellow oil (160 mg, 25%). ^{1}H-NMR (300 MHz $CDCl_3$) δ: 6.09 (d, J=3.0 Hz, 1H), 5.90 (m, 1H), 4.18 (q, J=6.9 Hz, 2H), 3.62 (s, 2H), 2.87 (s, 3H), 1.27 (t, J=6.9 Hz, 3H).

[3-(5-Methyl-2-furyl)-2-oxopropyl]phosphonate (10l) Compound **10l** was prepared in the same procedure as described of **10d** from **20a** as a pale yellow oil (128 mg, yield 53% in 3 steps). ^{1}H-NMR (300 MHz $CDCl_3$) δ: 6.11 (m, 1H), 5.91 (m, 1H), 3.84 (s, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.14 (d,

J=22.5 Hz, 2H), 2.26 (s, 3H).

Butyl 4-Iodobutanoate (17) To a stirred solution of *n*-butanol (100 ml) was added dropwise slowly thionyl chloride (14.9 ml, 204 mmol) at 0 °C (internal temperature: 5—47 °C) under argon atmosphere. After being stirred for 10 min, to this mixture was added a solution of 4-chlorobutanoic acid (25.0 g, 204 mmol) in *n*-butanol (20 ml). After being stirred at 60 °C for 5 h, the reaction mixture was cooled to room temperature, and was poured into ice, extracted with EtOAc/hexane, washed with water four times, saturated aqueous $NaHCO_3$, then brine, and dried over Na_2SO_4. The organic solvent was removed by evaporation to give an ester as a colorless oil (41.2 g).

To a stirred solution of above-described ester in CH_3CN (200 ml) was added sodium iodide (61.5 g, 410 mmol) at room temperature under argon atmosphere, and stirring was continued at 90 °C for 3 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 **17** as a yellow oil (57.5 g, 100%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.09 (t, J=7.2 Hz, 2H), 3.24 (t, J=7.2 Hz, 2H), 2.45 (t, J=7.2 Hz, 2H), 2.25—2.05 (m, 2H), 1.74—1.59 (m, 2H), 1.46—1.26 (m, 2H), 0.94 (t, J=7.2 Hz, 3H).

Butyl 4-({2-[(2*R*)-2-(Hydroxymethyl)-5-oxo-1-pyrrolidinyl]ethyl}thio)-butanoate (13) To a stirred solution of potassium tert-butoxide (701 mg, 6.25 mmol) in *n*-butanol (5 ml) and THF (5 ml) was added a solution of thioacetate **11** (1.89 g, 5.68 mmol) in THF (10 ml) at room temperature under argon atmosphere. After being stirred for 15 min, to a reaction mixture was added iodide **17**, and stirring was continued at for additional 30 min. The reaction was quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with MTBE, washed with H_2O twice, brine, and dried over $MgSO_4$. The organic solvent was removed by evaporation to give a sulfide **12**. A solution of above-described sulfide **12** in THF (15 ml) was treated with a solution of TBAF (1.0 M in THF, 6.82 ml, 6.82 mmol) at room temperature under argon atmosphere for 1 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 (EtOAc/MeOH, 1/0—95/5) to give **13** as a pale yellow oil (1.44 g, 80%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.07 (t, J=6.9 Hz, 2H), 3.73—3.39 (m, 5H), 2.79—2.26 (m, 10H), 2.24 (m, 1H), 2.00—1.86 (m, 3H), 1.70—1.55 (m, 2H), 1.78 (m, 2H), 0.94 (t, J=7.5 Hz, 3H).

Butyl 4-({2-[(2*R*)-2-Formyl-5-oxo-1-pyrrolidinyl]ethyl}thio)butanoate (14) Compound **14** was prepared from **13** according to the same procedure as described of **5a** from **4a** as a pale yellow oil, 64%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.10 (m, 3H), 6.67 (d, J=15.6, 7.8 Hz, 1H), 6.25 (dd, J=15, 6.0 Hz, 1H), 4.30 (m, 1H), 4.07 (t, J=6.9 Hz, 1H), 3.80 (s, 2H), 3.66 (m, 1H), 2.95 (m, 1H), 2.70—2.25 (m, 9H), 1.97—1.20 (m, 10H), 0.90 (t, J=7.5 Hz, 3H).

Butyl 4-{(2-{(2*R*)-2-[(1*E*)-4-(3-Ethylphenyl)-3-oxo-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio}butanoate (16a) Compound **16a** was prepared from **14** using **10k** instead of **10a** according to the same procedure as described of **8a** from **5a** as a colorless oil (251 mg, 57% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.22 (m, 1H), 7.12—7.00 (m, 3H), 5.77 (dd, J=15.4, 5.8 Hz, 1H), 5.52 (dd, J=15.4, 8.8 Hz, 1H), 4.41 (m, 1H), 4.12 (m, 1H), 4.07 (t, J=6.6 Hz, 2H), 3.63 (m, 1H), 2.98 (m, 1H), 2.91—2.77 (m, 2H), 2.68—2.48 (m, 6H), 2.44—2.35 (m, 4H), 2.23 (m, 1H), 1.97—1.86 (m, 2H), 1.80—1.58 (m, 3H), 1.46—1.34 (m, 2H), 1.23 (t, J=7.4 Hz, 3H), 098 (t, J=7.1 Hz, 3H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(3-ethylphenyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3c) Compound **3c** was prepared from **16a** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (122 mg, 92%). IR (film): 3389, 2929, 1660, 1417, 1234, 1103, 1032, 976, 796, 704, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.24 (m, 1H), 7.13—6.98 (m, 3H), 5.78 (dd, J=15.4, 5.5 Hz, 1H), 5.52 (ddd, J=15.4, 8.2, 1.1 Hz, 1H), 4.42 (m, 1H), 4.12 (m, 1H), 3.63 (m, 1H), 3.00 (m, 1H), 2.90—2.77 (m, 2H), 2.67—2.35 (m, 10H), 2.23 (m, 1H), 1.95—1.85 (m, 2H), 1.72 (m, 1H), 1.22 (t, J=7.4 Hz, 3H); MS (APCI) m/z: 404 $(M-H)^-$; HR-MS-FAB (m/z): $[M-H]^-$ Calcd for $C_{22}H_{30}NO_4S$, 404.1896; Found: 404.1910.

Butyl 4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(5-methyl-2-furyl)-1-buten-1-yl]-5-oxo-1-pyrrolidinyl}ethyl)thio]butanoate (16b) Compound **16b** was prepared from **14** using **10l** instead of **10a** according to the same procedure as described of **8a** from **5a** as a pale yellow oil (53 mg, 34% in 3 steps). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.99 (m, 1H), 5.87 (m, 1H), 5.75 (dd, J=15.3, 5.7 Hz, 1H), 5.55 (dd, J=15.3, 8.7 Hz, 1H), 4.43 (m, 1H) 4.20—4.03 (m, 3H), 3.64 (m, 1H), 3.05 (m, 1H), 2.95—2.10 (m, 15H), 1.98—1.35 (m, 7H), 0.93 (t, J=7.5 Hz, 3H).

4-[(2-{(2*R*)-2-[(1*E*,3*S*)-3-Hydroxy-4-(5-methyl-2-furyl)but-1-enyl]-5-oxopyrrolidin-1-yl}ethyl)sulfanyl]butanoic Acid (3k) Compound **3k** was prepared from **16b** according to the same procedure as described of **2b** from **8a** as a pale yellow oil (36 mg, 90%). IR (film): 3383, 2921, 1726, 1657, 1420, 1361, 1218, 1156, 1023, 974, 786, 754, 666 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 5.99 (d, J=3.0 Hz, 1H), 5.88 (m, 1H), 5.76 (dd, J=15.6, 5.7 Hz, 1H), 5.55 (ddd, J=15.6, 8.1, 1.2 Hz, 1H), 4.47 (m, 1H), 4.14 (m, 1H), 3.63 (m, 1H), 3.04 (m, 1H), 2.93—2.78 (m, 2H), 2.71—2.19 (m, 12H), 1.99—1.81 (m, 2H), 1.80—1.63 (m, 1H); MS (APCI) m/z: 380 $(M-H)^-$; HR-MS-FAB (m/z): $[M-H]^-$ Calcd for $C_{19}H_{26}NO_4S$, 380.1532; Found: 380.1550.

mEP1—4 Receptor Binding Assay Competitive binding studies were conducted using radiolabeled ligands and membrane fractions prepared from Chinese hamster ovary (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 Chinese hamster ovary (CHO) cells expressing mouse or 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).

LPS-Induced Changes in Plasma TNF-α Levels in Rats LPS was dissolved in a sterile saline solution (1 mg/ml), and the test compound was dissolved in a sterile saline solution containing 20% HP-β-CD. Then, the test compound was orally administered to seven-week-old Sprague-Dawley rats (Charles River, Japan). After 30 min, an intravenous administration of LPS (10 μg/2 ml/kg) was given, and 90 min after the LPS injection, blood samples were withdrawn into heparinized syringes *via* aortic puncture. Following centrifugation at 12000 rpm for 3 min at 4 °C, plasma was recovered and immediately frozen at 80 °C. Plasma TNF-α concentrations were determined *via* an enzyme-linked immunosorbent assay (ELISA) kit (Biosource).

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 1.0 or 0.5 mg/ml human/rat 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 15 or 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.

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