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An Improved Synthesis of the Selective EP4 Receptor Agonist ONO-4819

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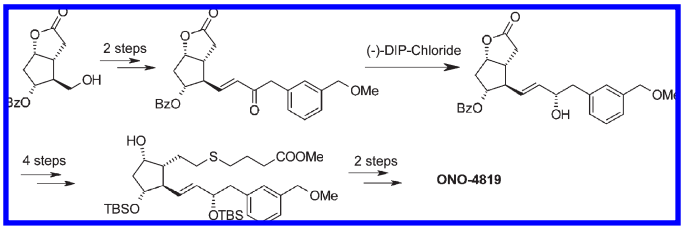

An improved synthesis of the highly selective EP4-receptor agonist **ONO-4819** has been developed. The previous synthesis suffered from several drawbacks, in which a critical one is the difficulty in the removal of byproducts leading to unsatisfactory quality of the active pharmaceutical ingredient (API). Furthermore, on stereoselective reduction of an enone intermediate by binaphthol-modified lithium aluminum hydride, low concentration of the reaction conditions and tedious purification procedures to remove excess binaphthol were critical issues for the manufacturing process of the API. In the improved process, we have developed improved conditions using γ-thiobutyrolactone as sulfur source instead of potassium thioacetate to introduce the sulfur-containing C4 side chain without formation of byproducts. For stereoselective synthesis of the chiral alcohol, (−)-DIP-chloride reduction is found to be the best method, which can improve not only the enantioselectivity but also the workload for removing the chiral modifier in a purification process. Furthermore, benzoyl and *tert*-butyldimethylsilyl groups as protecting groups for hydroxyl functions were used for precise process controls of all intermediates. By changing these protecting groups, the purity of **ONO-4819** was strictly controlled through crystalline intermediates. Thus, an improved robust process for **ONO-4819** with a high chemical purity was developed.

Introduction

Prostaglandins exhibit a broad range of physiological actions that are mediated by all of the receptor subtypes. The receptor of PGE_2 has been known to be classified into four subtypes, EP1, EP2, EP3, and EP4.[1] Among these subtypes, the EP4 receptor is an interesting pharmacological target because of its important regulatory effects in various physiological actions. Recently, it was reported that the highly selective agonist for prostaglandin E receptor subtype EP4 **ONO-4819** in combination with risedronate could be an effective treatment for osteoporosis.[2] The stereoselective synthesis of **ONO-4819** has also been reported using commercially available THP-protected Corey lactone **1**[3] as the starting material (Scheme 1).[4] In this process, the THP protecting group is a key to success for obtaining enone **4** in good to excellent yield, although it would not be suitable for quantitative analysis of its intermediate due to the formation of diasteromic THP ether.

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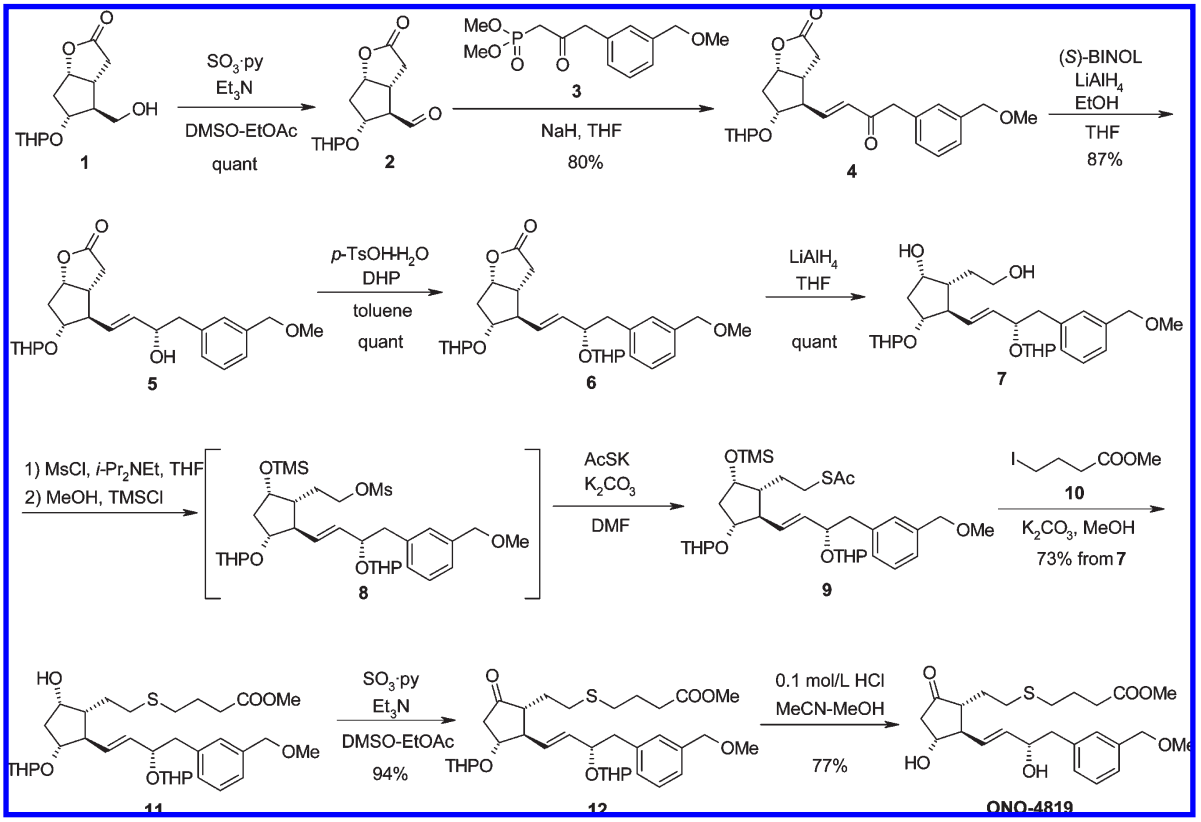
SCHEME 1. Early-Stage Synthesis for ONO-4819



Aldehyde **2** was synthesized from **1** with SO_3·py, and resulting **2** was submitted to a Honer−Emmons reaction with phosphonate **3** which was prepared from 3-methylphenylacetic acid in four steps,[5] gave an enone **4**. Stereoselective reduction of the enone **4** with binaphthol-modified lithium aluminum hydride (BINOL-H)[6] is a crucial step to control the chirality at C15 position of prostaglandins and it provided 15 (*S*)-alcohol **5** (84% de). Protection of the hydroxy group of **5** as a tetrahydropyranyl (THP) ether and the resulting bis-THP ether **6** underwent reduction of the γ-lactone moiety by lithium aluminum hydride gave a diol **7**. Compound **7** was converted into **9** by the following sequence: (i) methanesulfonylation of the primary alcohol, (ii) the protection of the secondary alcohol as a TMS ether, and (iii) the substitution of the resulting mesylate with potassium thioacetate to give thioacetate **9**. The resulting **9** was submitted to methanolysis followed by *S*-alkylated using methyl 4-iodobutanone **10** to afford alcohol **11**. Oxidation of the 9-hydroxyl group of **11** with SO_3·py complex afforded **12**. The deprotection of the THP group was achieved under acidic conditions. This early stage synthesis suffered from several drawbacks. First, protection of the hydroxy group as a THP ether formed several diastereomers which led to difficulty in developing suitable analytical methods for intermediates. Thus, the purity of intermediates and API could not be strictly controlled. Second, stereoselective reduction of **4** using BINOL-H reagent required low concentration conditions, and removal of the chiral ligand and Al was very troublesome for purification of **5**. Furthermore, using potassium thioacetate (AcSK) in the selective substitution of the primary alcohol group of **7** led to the formation of unremovable impurities (**31**−**33**) in **ONO-4819** (Scheme 5). We report here an improved robust process for ONO-4819 synthesis.

Results and Discussion

From the evaluation of the reported process[4] on a desk analysis, we identified several drawbacks of the process and focal points for our process development study. At the outset of our analysis, it was planned to change the protecting group of the starting material and intermediates from THP to others which do not form diastereomeric mixtures caused by the protecting group. We also focused on a stereoselective reduction of **15** to improve the stereoselectivity and the workload in the viewpoint of process time reduction and time/volume efficiency. Furthermore, to avoid the formation of impurities which are difficult to remove from the API, transformation from **19** to **20**, we decided to modify the process by introducing a thiobutylic acid unit, and we selected γ-thiobutyrolactone as the reagent of the sulfur-containing unit. By applying these tactics to the synthesis of **ONO-4819**, an improved synthesis of **ONO-4819**, in which bis-TBS product **18** serves as a key intermediate, was achieved with significantly improved chemical purity (Scheme 2).

Preparation of a Key Intermediate 18. The early-stage synthesis started from THP-protected Corey lactone **1** in which the THP moiety leads to the formation diastereomeric

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SCHEME 2. Improved Process for ONO-4819

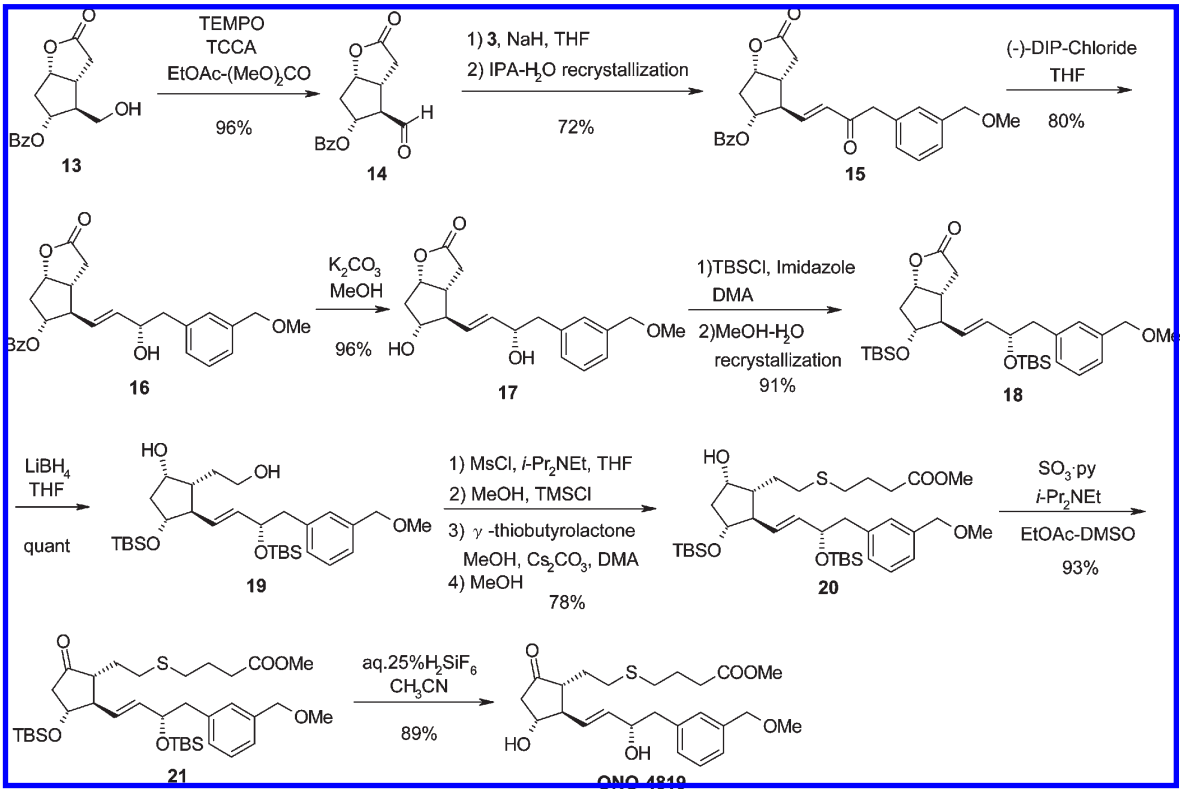
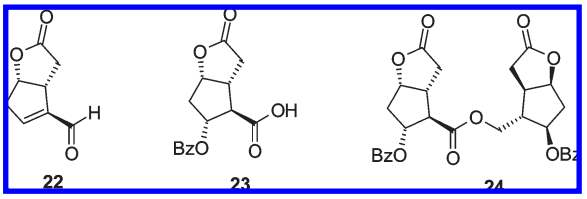


TABLE 1. Various Quenching Conditions for Oxidation Reaction of 13

entry	reagent	yield of **14**,[a] %
1	EtOH	ND[b]
2	aq satd $NaHSO_3$	60
3	aq satd $Na_2S_2O_3$	88
4	aq $Na_2S_2O_3$ and K_2HPO_4	90

[a]Isolated yield. [b]ND: not determined.

intermediates, so we selected a commercially available benzoyl (Bz)-protected Corey lactone **13** as a starting material. As might be expected, **14** was chemically unstable under basic conditions, and oxidation of **13** using $SO_3 \cdot$py complex or Moffat oxidation conditions (DCC, $Cl_2HCCOOH$ or H_3PO_4)[7] afforded an undesired enal byproduct **22**. Moreover, **14** which is a β-alkoxy aldehyde, is also expected to be easily hydrated. In practice, 2,2,6,6-tetramethyl-1-piperidinyloxy, radical (TEMPO) oxidation using aqueous NaOCl solution as a co-oxidant led to undesired carboxyl product **23**. An efficient conversion of **13** to **14** was accomplished by TEMPO oxidation under nonaqueous conditions using trichloroisocyanuric acid (TCCA)[8] as a co-oxidant in a mixture of EtOAc and $(MeO)_2CO$. Addition of starting material **13** to the mixture of TEMPO and TCCA was necessary to avoid formation of the undesired ester **24** via a hemiacetal intermediate. The successful outcome of this reaction was also assisted by the quenching conditions of any excess oxidant in the isolation of aldehyde **14** (Table 1). Quenching with EtOH gave complex mixture (entry 1). Using aqueous $NaHSO_3$ solution led to the formation of the $NaHSO_3$ adduct to aldehyde **14** which needed strong basic conditions to form free aldehyde **14** (entry 2). Although treatment of the reaction mixture with aqueous $Na_2S_2O_3$ solution led to decomposition of $Na_2S_2O_3$ and provided undesired **23**, treatment with aqueous $Na_2S_2O_3$ solution including K_2HPO_4 gave good results under neutral condition (pH 7) (entries 3 and 4).



Horner−Emmons reaction of the aldehyde **14** with phosphonate **3** afforded an enone **15** as a crystalline intermediate. The impurities generated in the Horner−Emmons reaction were completely removed during column chromatography and recrystallization, thus enabling the quality of the enone product to be well controlled. In the previous synthesis, an equimolar amount of BINOL-H reagent was used for the stereoselective reduction of enone **15** in which tedious removal procedures for Al and chiral ligand were needed. A large amount of aqueous sodium hydrogen (+)-tartrate solution was required at workup to remove the Al residue, and a large amount of SiO_2 was also used to remove (*S*)-BINOL by chromatography. We first examined other stereoselective reduction conditions with a catalytic amount of (*R*)-methyloxazaborolidine ((*R*)-Me-CBS) and borane−dimethyl sulfide complex (BMS), which led to good selectivity (80% de) and a simple isolation procedure

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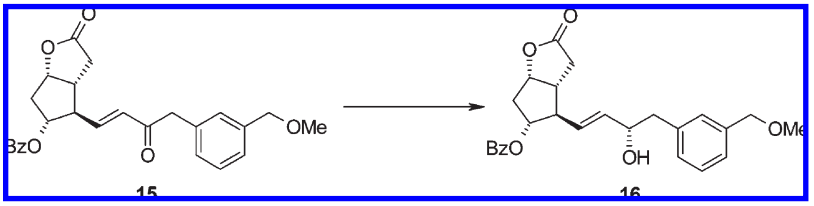
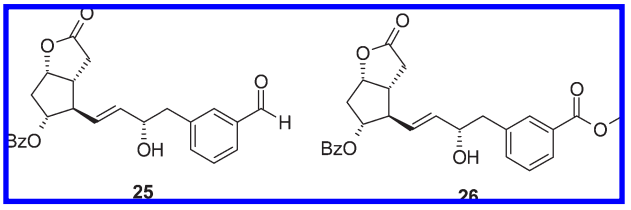
TABLE 2. Various Stereoselective Reductions for 15



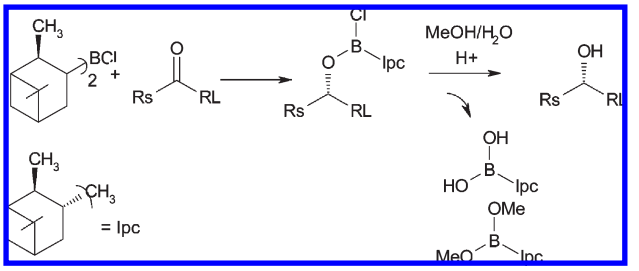
entry	conditions	*T*, °C	time, h	conv of **16**,[a] %	de of **16**,[b] %
1	(*S*)-BINOL (1 equiv), EtOH (1 equiv), $LiAlH_4$ (1 equiv), THF	−78	2	92	81
2	(*R*)-Me CBS (0.1 equiv), PhOH (1 equiv), BH_3Me_2S (1 equiv), toluene	0	5	94	80
3	(−)-DIP-chloride (1.2 equiv), THF	0	2	90	87
4	(−)-DIP-chloride (2 equiv), THF	0	2	98	83
5	(−)-DIP-chloride (2 equiv), THF	−20	5	98	87
6	(−)-DIP-chloride (2 equiv), THF	−40	9	96	90
7	L-TarB-NO_2 (2 equiv), $NaBH_4$ (2.0 equiv), THF	0	24	95	−8
8	$RuCl_2$[(*R*)-binap][(*R*)-daipen[c]] (5 mol %), HCOOH (2.4 equiv), Et_3N (2.4 equiv), MeCN	rt	24	NR[d]	
9	$RuCl_2$ [(*R*)-binap] [(*R*)-daipen] (5 mol %) H_2 0.8 MPa, K_2CO_3 (20 mol %), IPA−THF	rt	24	trace	

[a]The conversion was determined by HPLC analysis. [b]The stereoselectivitiy of product **16** was calculated from chiral HPLC analysis (CHIRALCEL OD-RH; MeCN/H_2O = 30:70; an UV at 210 nm; flow rate, 1.0 mL/min; retention time, 53.9 min (*β*-OH), 63.4 min (**16**). [c]daipen: 1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine. [d]NR: no reaction.

(extraction and column chromatography). As this reduction was found to be difficult in terms of the reproducibility on a large scale due to the need for severe control of water content,[9] we further investigated other reduction conditions. These results are shown in Table 2. (−)-*B*-chlorodiisopinocampheylboranes ((−)-DIP-chloride)[10] achieved a superior stereoselectivity (entries 3−5), and the best selectivity was recognized at the temperature around −40 °C (entry 6). Reduction with $NaBH_4$ with a catalytic amount of L-TarB-NO_2,[11] derived from tartaric acid, gave poor diastereoselectivity (entry 7). Hydrogenation and transfer hydrogenation conditions with chiral Ru complexes did not proceed (entries 8 and 9).[12,13] Although we chose (−)-DIP-chloride as a reductant for reduction of enone **15**, there was a problem that crude alcohol product **16** was unstable and generated a substantial amount (~6%) of byproducts **25** and **26** during storage of **16** even under an Ar atmosphere. These byproducts came from the oxidation of the benzylic carbon of alcohol **16**.



SCHEME 3. Proposed Mechanism for Formation of Byproducts in the Reduction of Ketone with DIP-chloride



There are two main methods for workup after reduction of prochiral ketones with (−)-DIP-chloride: the method of quenching excess reductant with acetaldehyde and the nonoxidative removal of the boron byproduct as the diethanolamine complex.[14] However, these workup procedures could not prevent the formation of byproducts **25** and **26**. No improvement in stability of **16** was observed after washing the reaction mixture with various aqueous solutions (aq 5% $Na_2S_2O_3$, aq 9% $NaHCO_3$, aq tartaric acid, aq 1 M HCl, aq 15% NH_4Cl, aq 1 M NaOH, aq 9% $NaHCO_3$, H_2O). We assumed that quenching the reaction with MeOH or H_2O formed α-pinene-$B(OH)_2$ or α-pinene-$B(OMe)_2$, each of which have a boron−carbon bond and which could work as radical initiators in a manner similar to that for triethylborane[15] (Scheme 3). To verify this hypothesis, we investigated the effects of these compounds on the instability of alcohol **16**. The results are summarized in Table 3. Addition

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TABLE 3. Stability Test of 16 under Various Conditions[a]

			HPLC area ratio		
entry	additives	time	**16**	**25**	**26**
1[b]	none	initial	98.9	0.22	ND[d]
		1week	87.1	4.2	1.9
2	none	initial	97.7	0.65	ND
		1week	97.7	0.62	ND
3	*i*-PrB(OH)$_2$	initial	98.9	0.42	0.27
		1week	98.7	0.57	0.34
4	Et_3B	initial	98.5	0.14	0.29
		1week	97.2	0.96	0.47
5[b,c]	BHT	initial	96.0	0.07	ND
		1week	96.3	0.01	ND

[a]All reactions were conducted by the same procedure unless otherwise noted. To purified **16** by SiO_2 column chromatography was added 1 equiv of additives and the mixture stored under Ar atmosphere at 0 °C for 1 week. [b]Crude **16** was used. [c]0.01 equiv of BHT was added. [d]ND: not detected.

of triethylborane or isopropylboronic acid instead of α-pinene-B(OH)$_2$ and α-pinene-B(OMe)$_2$ to purified alcohol **16** led to increased levels of byproducts **25** and **26** (entries 3 and 4), whereas 0.01 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) completely prevented the formation of **25** and **26** (entry 5). These observations support the above assumption that **16** was autoxidized in the presence of a radical initiator, and autoxidation of **16** was not suppressed completely under an Ar atmosphere.

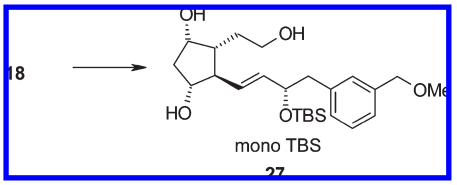
Conversion of **16** to **17** was accomplished by methanolysis in the presence of K_2CO_3 and MeOH. In the next step, the *tert*-butyldimethylsilyl (TBS) group was chosen to protect two hydroxyl groups in **17** because the TBS group allows no formation of diastereomeric isomers and is also stable through the conversion of **18** to **21**. Bis-silylation was achieved with *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole and gave the desired product **18** as crystals, which were purified by recrystallization.

From examination of the results so far, we chose the benzoyl and TBS groups to protect hydroxyl functions on intermediates. The purity of **18** could be controlled through two crystalline intermediates (**15** and **18**) by recrystallization up to 97.0 area %. Stereoselective reduction of **15** with (−)-DIP-chloride improved the enantioselectivity. With these methods, **18** could be obtained in high chemical yield. The bissilylated product **18** was used as a key intermediate to control the quality of **ONO-4819**.

Preparation of ONO-4819. In the previous synthesis of **ONO-4819**, lactone **6** was successfully reduced to diol **7** with $LiAlH_4$. However, the reduction of **18** under the same reduction conditions did not give the desired diol **19** but the desilylated triol **27** (Scheme 4). Fortunately, the desired conversion was achieved by using $LiBH_4$ as reductant to give **19** in quantitative yield.

In the early procedure, conversion of **7** to **11** was conducted by the sequence: (i) methanesulfonylation of the primary alcohol of **7**, (ii) the substitution of the methanesulfonate with potassium thioacetate, (iii) methanolysis of the resulting thioacetate **9** with K_2CO_3 and MeOH, followed by *S*-alkylation of the resultant thiol with methyl 4-iodobutanoate **10** to give **11**. On this transformation, three troublesome byproducts (**28**, **29**, and **30**) were formed, which were converted to **31**, **32**, and **33** through the sequence to **ONO-4819** (Scheme 5). These compounds were difficult to be removed from **ONO-4819** even with

SCHEME 4. $LiAlH_4$ Reduction of 18



SCHEME 5. Impurities in 11 and ONO-4819

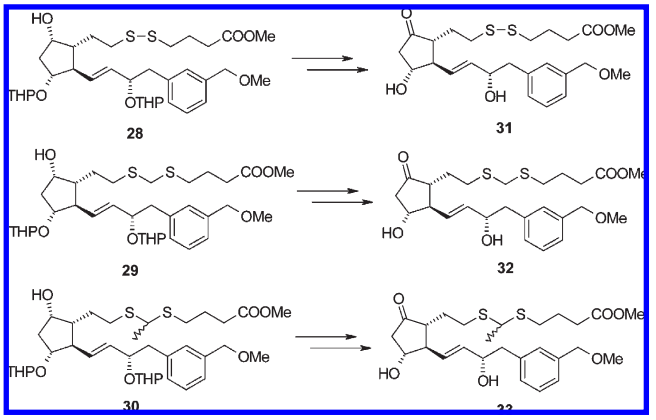
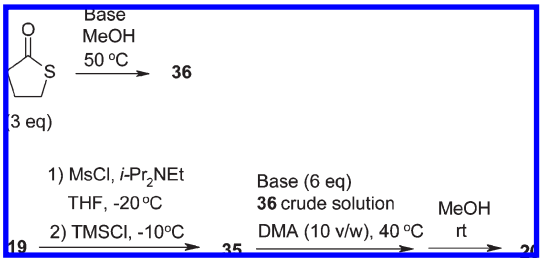


TABLE 4. Initial Screening of Bases for the Substitution Reaction of 35[a]



entry	base	yield of **20**,[b] %
1	*t*-BuOK	39
2	NaOMe	0
3	Cs_2CO_3	83
4	K_2CO_3	55

[a]To the reaction mixture of **35** was added a solution of methyl 4-mercaptobutanoate **36**. [b]Isolated yield.

repeated column chromatography purification. Although the mechanism of the formation of **28**, **29**, and **30** was unclear, we speculated the problem came from the quality of potassium thioacetates, since different lots of potassium thioacetates gave different impurity profiles on **11**. It was decided to attempt the γ-thiobutyrolactone as a reagent to introduce a sulfur moiety under the following reaction conditions.

Detail of the sequence **19** to **20** using γ-thiobutyrolactone is shown in Scheme 6. Diol **19** was conducted by selective methanesulfonylation of the primary alcohol, and the remaining secondary alcohol in **34** was protected with TMS to provide **35**. To the mixture of **35** was added methyl 4-mercaptobutanoate **36**, prepared from γ-thiobutyrolactone in the presence of base and methanol. Because compound **36** has a strong odor, it was necessary to use a next step without

SCHEME 6. Improved Method of Conversion from 19 to 20

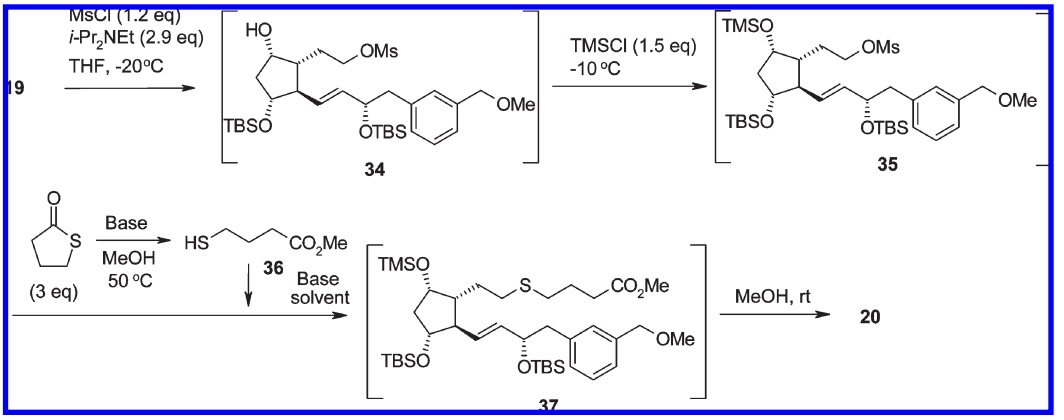


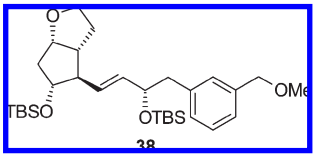
TABLE 5. DOE Experiment for Formation of 20: Experimental Matrix and Measured Response

entry	T, °C	base[a]	solvent (v/w)	yield of **20**,[b] %
1	25	K_2CO_3	DMA (4)	8
2	25	Cs_2CO_3	DMI (4)	76
3	25	K_2CO_3	DMI (4)	20
4	25	Cs_2CO_3	DMA (8)	76
5	40	K_2CO_3	DMI (4)	19
6	40	Cs_2CO_3	DMA (4)	83
7	40	K_2CO_3	DMA (8)	10
8	40	Cs_2CO_3	DMI (8)	73

[a]4 equiv of base was used. [b]Isolated yield.

isolation in a pilot scale synthesis. Deprotection of **37** with additional MeOH gave the desired thioether **20**.

Generally, methyl 4-mercaptobutanoate **36** was prepared from γ-thiobutyrolactone using relatively expensive bases (*t*-BuOK, NaOMe).[16,17] We initially screened the conditions of the preparation of **36** followed by substitution reaction of **35** with several bases. The results are summarized in Table 4. K_2CO_3 and Cs_2CO_3 were found to be superior to *t*-BuOK and NaOMe for this transformation. Because of the strong basicity of *t*-BuOK, undesired ether byproduct **38** was formed in ~45% yield via deprotection of the TMS group on intermediates **35**. We chose K_2CO_3 and Cs_2CO_3 for further optimization of the reaction conditions.



The optimization was conducted by a design of experiment (DOE) with base (Cs_2CO_3 and K_2CO_3), solvent (DMA and DMI), solvent volume (4 v/w and 8 v/w), and temperature (25 and 40 °C) as the variables (Table 5) in the transformation from **35** to **20**. Initial experiments using aprotic solvent which has high boiling points increased reaction rate, so DMA and DMI were selected for further study. These variables were studied on 2^{4-1} fractionated factorial design (eight experiments) without center points. As a result of DOE experiments, a strong main effect was recognized in the base; Cs_2CO_3 is preferable to K_2CO_3. Since K_2CO_3 has low solubility in aprotic solvents, it decreased the rate of substitution reaction for **35** with **36**. Extended reaction time led to the formation of **38** through the cleavage of the TMS group on intermediates **35**, followed by intramolecular reaction of the 9-hydroxyl group and 5-methanesulfonyl group. In addition, K_2CO_3 led to low reproducibility of results in several experiments on the substitution reaction due to the solid/liquid heterogeneous conditions. Although no difference was found between DMA and DMI on the yield of **20**, DMA was chosen as it was easily removed by washing the reaction mixture with water. There was an inverse relationship between the volume of solvent and the temperature. When 4 v/w of solvent was used, higher temperature gave a good result, whereas a lower temperature worked well with 8 v/w solvent. For the scaled-up synthesis, the lower batch volume was likely to be more efficient, so 4 v/w of solvent was selected for this reaction. Using these optimized conditions of 4 equiv of Cs_2CO_3, at 40 °C in 4 v/w of DMA, the key transformation from **35** to **20** was successfully demonstrated to give **20** in 80% yield with no formation of byproducts.

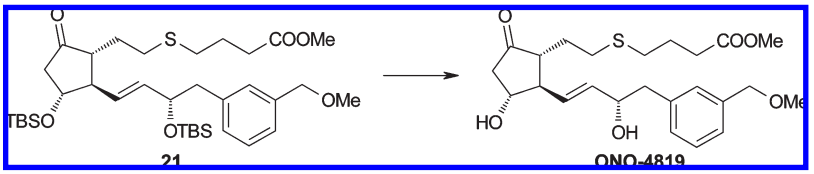
According to the early-stage synthesis, the 9-hydroxyl group of **20** was successfully oxidized with $SO_3 \cdot$py complex in DMSO and *i*-Pr_2NEt to afford 9-keto derivative **21** in good yield. In the final deprotection reaction, degradation of **ONO-4819** to PGA-type **40** was a serious problem. To suppress the degradation, we investigated various deprotection conditions (Table 6). Deprotection using TBAF was found to give a complex mixture (entry 1). Deprotetion with HF·py could be carried out under milder conditions and gave **ONO-4819** as the major product, however, the reaction required use of large excess reagent and the formation of a small amount of undesired **40** was observed (entry 2). Fluorosilicic acid (H_2SiF_6) is known to be less acidic than HF, which means that certain acid-labile groups can be retained under the deprotection conditions.[18] The deprotection reaction with aq 25% H_2SiF_6 in MeCN at 0−10 °C proceeded along with a trace amount of **40** (entries 3 and 4). Using these optimized conditions, deprotection of TBS groups on **21** was achieved to give **ONO-4819** in 89% yield, 99.5% purity. The key to the suppression of the impurities in **ONO-4819** was

(16) Elworthy, T. R.; Brill, E. R.; Chiou, S. S.; Chu, F.; Harris, J. R.; Hendricks, R. T.; Huang, J.; Kim, W.; Lach, L. K.; Mirzadegan, T.; Yee, C.; Walker, K. A. M. *J. Med. Chem.* **2004**, *47*, 6124.

(17) Barraclough, P.; Bolofo, M. L.; Giles, H.; Gillam, J.; Harris, C. J. *Bioorg. Med. Chem.* **2002**, *10*, 2103.

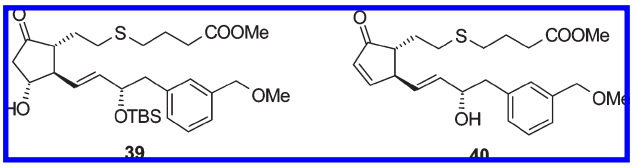
(18) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.

TABLE 6. Deprotection of TBS Groups in 21 under Various Conditions



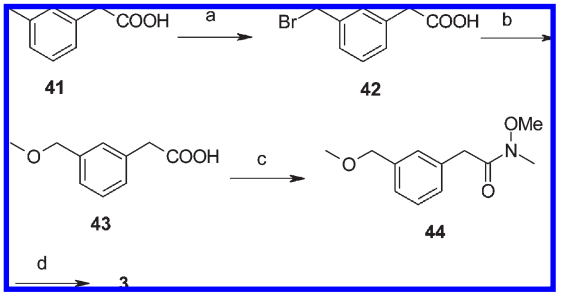
				HPLC area ratio			
entry	conditions	*T*, °C	time, h	**ONO-4819**	**21**	**39**	**40**
1	TBAF (3 equiv), AcOH (2.1 equiv), DMF−H_2O	10 to rt	2	complex mixture			
2	HF-Py (large excess), THF	0 to rt	3	94.9	ND	ND	5.1
3	aq 25% H_2SiF_6 (1.0 equiv), MeCN	0	8	94.1	2.9	0.1	0.8
4	aq 25% H_2SiF_6 (1.0 equiv), MeCN	10	6	96.2	ND	ND	1.9
5	aq 25% H_2SiF_6 (1.0 equiv), MeCN	25	4	84.9	ND	ND	10.7

the development of an improved method for transformation from **19** to **20** through a key intermediate **18**.



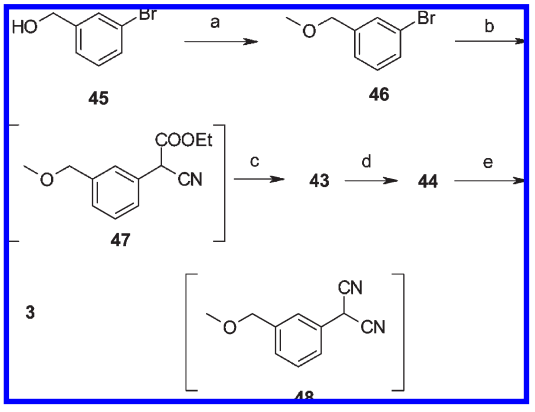
Finally, improvement of the synthesis of phosphonate **3** was addressed. The initial route to **3**, which was prepared from 3-methylphenylacetic acid in four steps, has some area for improvement (Scheme 7). Bromination of **41** with *N*-bromosuccinimide (NBS) and 2,2′-azobisisobutyronitrile (AIBN) provided a low yield of **42**. Moreover, the cost of starting material **41** and the environmental issues associated with the use of CCl_4 were highly undesirable. With these considerations, we decided to explore the efficient synthesis of **3**, which was prepared from inexpensive 3-bromobenzyl alcohol **45** in four steps using a coupling reaction between aryl halide and ethyl cyanoacetate as a key step (Scheme 8). Methylation of **45** with Me_2SO_4 and KOH provided **46** in good yield. Methyl ether **46** underwent coupling with ethyl cyanoacetate in the presence of palladium catalyst, and the ethyl cyanoacetate moiety in compound **47** was hydrolyzed

SCHEME 7. Previous Synthetic Route to 3[a]



[a]Reagents: (a) *N*-bromosuccinimide (NBS), 2,2′-azobisisobutyronitrile (AIBN), CCl_4, 0 °C, 31%; (b) NaOMe, MeOH, reflux, 99%; (c) *N*,*O*-dimethylhydroxylamine hydrochloride, 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide monohydrochloride (EDC), 1-hydroxybenzotriazole (HOBt) monohydrate, *N*-methylmorpholine, CH_2Cl_2, rt, 92%; (d) dimethyl methylphosphonate, *n*-BuLi, toluene, −74 °C, then SiO_2 chromatography, 64%.

SCHEME 8. Synthesis of 3[a]



[a]Reagents: (a) Me_2SO_4, KOH, THF, 92%; (b) ethyl cyanoacetate, $Pd(PPh_3)_4$, NaH, THF, reflux; (c) NaOH, reflux, 4 h, 94% from **46**; (d) *N*,*O*-dimethylhydroxylamine hydrochloride, EDC, Et_3N, CH_3CN, 93%; (e) dimethyl methylphosphonate, *n*-BuLi, toluene, 76%.

and decarboxylated to **43** under reflux conditions for 4 h. In the sequence from **46** to **43**, when malononitrile was used as a coupling partner of **46**, it took 3 days to hydrolyze and decarboxylate the malononitrile moiety in **48**. Thus, the synthetic route using ethyl cyanoacetate was found to be much more efficient than that using malononitrile.

Conclusions

We have developed an improved synthetic process for the highly selective EP4-receptor agonist **ONO-4819**, using commercially available Corey lactone benzoate as a starting material. Successful stereoselective reduction of an enone intermediate was achieved using (−)-DIP-chloride instead of problematic binaphthol-modified lithium aluminum hydride. In the introduction of the thiobutylic acid unit in **ONO-4819**, γ-thiobutyrolactone was chosen as a sulfur-containing reagent and the reaction conditions were optimized by DOE in order to avoid byproduct formation. In this improved synthesis, benzoate and TBS were chosen as protecting groups, which allowed two intermediates to be crystallized. The purity of **ONO-4819** was highly controlled through the two crystalline intermediates and quantitative

analysis of all intermediates. Thus, an improved reproducible synthetic process for **ONO-4819** with a high chemical purity was developed.

Experimental Section

(3a*R*,4*R*,5*R*,6a*S*)-4-Formyl-2-oxohexahydro-2*H*-cyclopenta[*b*]-furan-5-yl benzoate 14. To a solution of trichloroisocyanuric acid (67.3 g, 109 mmol) in a mixed solution of dimethyl carbonate (373.5 mL) and ethyl acetate (76.5 mL) was added a Corey lactone **13** (6.00 g, 21.8 mmol) and TEMPO (170 mg, 1.09 mmol) at 0−5 °C under argon atmosphere. After the resulting slurry was stirred for 30 min, residual alcohol (24 g, 87 mmol) was added every 30 min in four portions at 0−5 °C. After the slurry was stirred for 30 min, the reaction mixture was slowly poured into a solution of $Na_2S_2O_3$ (64.4 g, 407 mmol), K_2HPO_4 (142 g, 815 mmol), and water (675 mL) at 0−10 °C. After the slurry was stirred for 1 h, the suspension was filtered through a pad of Celite and washed with dimethyl carbonate (90 mL). The organic layer was separated, washed with aq 20% NaCl solution (60 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to afford the desired aldehyde **14** (28.5 g, 95.6%, 94.9 HPLC area %) as a pale yellow powder: mp 123.5−125.5 °C; R_f 0.37 (EtOAc/*n*-hexane, 1/2); $[\alpha]^{20}_D$ −96.2 (*c* 1.22, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.01 (dd, 2H, J = 8.4, 1.5 Hz), 7.53 (m, 3H), 5.78 (d, 1H, J = 5.3 Hz), 5.16 (t, 1H, J = 6.3 Hz), 3.56 (m, 1H), 3.21 (m, 1H), 3.01 (dd, 1H, J = 18.5, 10.8 Hz), 2.53 (d, 1H, J = 16.1 Hz), 2.50 (dd, 1H, J = 18.4, 2.7 Hz), 2.08 (dt, 1H, J = 15.8, 5.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.4, 176.0, 166.0, 133.7, 129.8, 129.0 (2C), 128.7 (2C), 84.7, 75.4, 65.6, 38.3, 36.9, 36.0; IR (KBr) 2838, 1182, 1718, 1733, 1762, 722 cm^{-1}; MS (ESI, Pos., 40 V) *m*/*z* 297 (M + Na). HPLC conditions: YMC-Pack-C4-A-802, gradient (2 mmol *n*-dodecyltrimethylammonium chloride (DTMACl) in 20 mM KH_2PO_4 aq (pH = 3)/MeCN = 70/30)/(2 mmol DTMACl in 20 mM KH_2PO_4 aq (pH = 3)/MeCN = 50/50) = 100/0 (0−10 min) → 10%/min → 0/100 (20−40 min), detection, 250 nm; column temperature, 10 °C; flow rate, 1.0 mL/min; retention time of **14** was 9.3 min and that of **13** was 7.0 min.

(3a*R*,4*R*,5*R*,6a*S*)-4-[(1*E*)-4-[3-(Methoxymethyl)phenyl]-3-oxo-1-buten-1-yl]-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl Benzoate 15. To a stirred suspension of sodium hydride (61.1% in oil, 13.9 g, 348 mmol) in THF (2.61 L) was added a solution of dimethyl 3-[(3-methoxymethyl)phenyl]-2-oxopropanephosphonate **3** (109 g, 381 mmol) in THF (391 mL) at room temperature under Ar. After the resulted mixture was stirred for 1 h, to the resulting suspension was added a solution **14** (87.0 g, 317 mmol) in THF (1 L). The mixture was stirred for 30 min before the addition of acetic acid (19.9 mL, 348 mmol). The resulting yellow solution was diluted with EtOAc (1740 mL) and washed with water (1740 mL). The separated aqueous layer was extracted with EtOAc (870 mL), and the combined organic layers were washed with aq 20% NaCl solution (870 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (BW-235S, 2756 g, *n*-heptane/EtOAc = 1:1) to give crude **15** as a pale yellow powder (110 g). The mixture of crude **15** (78 g, 180 mmol) in IPA (936 mL) and water (936 mL) was warmed and completely dissolved at 50−55 °C, the resulting clear solution was cooled to 40 °C, and then the seed **15** (78 mg) was added. After being stirred for 30 min at 40 °C, the suspension was cooled to 5 °C at a speed of 20 °C/h. The resulting white crystal was filtered off, washed with ice-cooled water (780 mL), and dried under vacuum at 40 °C to afford **15** as a white powder (72 g, 73.7% from **14**, 98.3 HPLC area %): R_f 0.42 (EtOAc/*n*-hexane, 1/2; mp 75−77 °C; $[\alpha]^{20}_D$ −89.1 (*c* 0.50, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97 (dd, 2H, J = 8.2, 1.5 Hz), 7.59 (m, 1H), 7.45 (m, 2H), 7.19 (m, 4H), 6.75 (dd, 1H, J = 15.8, 7.7 Hz), 6.27 (d, 1H, J = 15.8 Hz), 5.28 (dt, 1H, J = 5.9, 5.3 Hz), 5.07 (m, 1H), 4.41 (s, 2H), 3.81 (s, 2H), 3.38 (s, 3H), 2.86 (m, 3H), 2.53 (m, 2H), 2.28 (ddd, 1H, J = 15.4, 4.7, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 176.1, 166.0, 144.0, 139.1, 134.2, 133.7, 130.5, 129.9, 129.4 (2C), 129.0 (2C), 128.9 (2C), 128.8 (2C), 126.7, 83.4, 78.7, 74.6, 58.5, 54.2, 48.6, 42.8, 38.0, 35.1; IR (KBr) 718, 1105, 1174, 1275, 1682, 1718, 1766, 2983 cm^{-1}; MS (ESI, Pos., 20 V) *m*/*z* 457 (M + Na). Anal. Calcd for $C_{26}H_{26}O_6$: C, 71.87; H, 6.03. Found: C, 71.90; H, 5.78. HPLC conditions: YMC-Pack-C4-A-802, A: MeCN, B: 20 mM KH_2PO_4 (pH = 3) A/B = 45/55 detection, 230 nm; flow rate, 1.0 mL/min; retention time of **15** was 18.3 min.

(3a*R*,4*R*,5*R*,6a*S*)-4-[(1*E*,3*S*)-3-Hydroxy-4-[3-(methoxymethyl)-phenyl]-1-buten-1-yl]-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-5-yl Benzoate 16. To a solution of enone **15** (3.0 g, 6.9 mmol) in THF (18 mL) was added slowly (−)-DIP-chloride (1.7 M in hexane, 8.1 mL, 14 mmol) at −20 °C. After the mixture was stirred for 2 h, BHT (304 mg, 1.38 mmol) was added to a reaction mixture. The solution was quenched with a mixed solution of MeOH (1.4 mL) and water (1.4 mL) at −20 °C. After being stirred for 30 min, the solution was diluted with MTBE (18 mL). To the resulting solution was added aq 1 M HCl. solution (9 mL) and stirred for 30 min at room temperature. Separated aqueous layer was extracted with MTBE (12 mL) and the combined organic layers was washed with aq. 10% K_2HPO_4 solution (15 mL), aq. 20% NaCl solution (6 mL), and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (BW-235S, 111 g, toluene/EtOAc, 3/2) to give crude **16** as a colorless oil (2.71 g, 80.0%, 90.8% de, 99.3 HPLC area %) . R_f 0.34 EtOAc/*n*-hexane, 1/2); $[\alpha]^{20}_D$ −35.2 (c 1.04, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 2H, J = 8.4, 1.3 Hz), 7.59 (m, 1H), 7.57 (m, 1H), 7.45 (m, 2H), 5.55 (ddd, 1H, J = 15.5, 7.2, 1.1), 5.20 (m, 1H), 5.03 (td, 1H, J = 6.5, 1.8 Hz), 4.42 (s, 2H), 4.35 (m, 1H), 3.40 (s, 3H), 2.78 (m, 5H), 2.51 (m, 2H), 2.21 (ddd, 1H, J = 15.5, 4.9, 1.9); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.5, 166.1, 138.6, 137.7, 135.0, 133.4, 129.7, 129.6, 129.0, 128.92 (2C), 128.88 (2C), 128.6 (2C), 83.4, 79.3, 74.7, 72.9, 58.4, 54.0, 44.0, 42.7, 37.7, 35.0; IR (liquid film) 3449, 2927, 1771, 1715, 1275, 1110, 714 cm^{-1}; Mass (ESI, Pos., 20 V) *m*/*z* 459 (M + Na); Anal.Calcd. for $C_{26}H_{28}O_6$: C, 71.54; H, 6.34; Found: C, 71.71; H, 6.34.; HPLC conditions for the determination of diastereoselectivity: CHIRALCEL OD-RH; MeCN:H_2O = 30/70 (0−90 min); detection, 210 nm; flow rate, 1.0 mL/min; retention time of **16** was 63.4 min, and that of β−OH was 53.9 min; HPLC conditions: YMC-Pack-ODS-A-302; MeCN/H_2O = 45/55 detection, 210 nm; column temperature, 40 °C; flow rate, 1.0 mL/min; retention time of **16** was 9.2 min, and that of **15** was 13.6 min.

(3a*R*,4*R*,5*R*,6a*S*)-5-Hydroxy-4-{(1*E*,3*S*)-3-hydroxy-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}hexahydro-2*H*-cyclopenta[*b*]furan-2-on 17. To a solution of alcohol **16** (47.1 g, 108 mmol) in MeOH (236 mL) was added K_2CO_3 (4.48 g, 32.4 mmol) at room temperature. After stirring for 2.5 h at 40 °C, the solution was cooled to 0−5 °C. To a solution was added 4 M HCl solution in EtOAc (21.6 mL, 86.4 mmol) to control pH under 3. The solution was diluted with EtOAc (94 mL) and the resulting slurry was filtered off through the pad of Celite and washed with EtOAc (47 mL). The solvent was removed by evaporation and to the resulted residue was added EtOAc (94 mL) and azeotropically concentrated. The residue was purified by column chromatography on silica gel (C-200, 940 g, EtOAc) to give crude **17** as a colorless oil (32.0 g, 89.4%, 90.8% de, 97.7 HPLC area%). R_f 0.23 (EtOAc); $[\alpha]^{20}_D$ +20.2 (c 1.28, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.18 (m, 2H), 7.11 (m, 1H), 5.64 (dd, 1H, J = 15.3, 6.3 Hz), 5.37 (dd, 1H, J = 15.4, 8.4 Hz), 4.84 (td, 1H, J = 7.1, 3.2 Hz), 4.42 (m, 2H), 4.33 (td, 1H, J = 6.4, 5.7 Hz), 3.84 (td, 1H, J = 7.9, 7.3 Hz), 3.41 (s, 3H), 2.83 (m, 2H),

2.66 (dd, 1H, J = 18.1, 9.5 Hz), 2.48 (m, 2H), 2.36 (dd, 1H, J = 18.1, 1.7 Hz), 2.22 (q, 1H, J = 8.5 Hz), 1.90 (ddd, 1H, J = 14.7, 8.2, 3.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.9, 138.3, 137.7, 135.5, 130.6, 129.2 (2C), 128.6, 126.2, 82.4, 76.3, 74.9, 73.2, 58.5, 56.2, 43.9, 42.5, 39.8, 34.1; IR (KBr) 3406, 3010, 2932, 1762, 1091, 755 cm^{-1}; Mass (ESI, Pos., 20 V) m/z 355 (M + Na); Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28; Found: C, 68.29; H, 7.60; HPLC conditions: YMC-Pack-ODS-A-302; MeCN/H_2O = 20/80 (0−20 min) → 2%/min (20−35 min) → 50/50 (35−45 min); detection, 210 nm; flow rate, 1.0 mL/min; retention time of **17** was 17.6 min, and that of 15-β was 15.6 min.

(3a*R*,4*R*,5*R*,6a*S*)-5-{[Dimethyl(2-methyl-2-propanyl)silyl]oxy}-4-{(1*E*,3*S*)-3-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}hexahydro-2*H*-cyclopenta[*b*]furan-2-one 18. To a solution of diol **17** (3.0 g, 8.8 mmol) and imidazole (15.6 g, 22.9 mmol) in DMA (17.5 mL) was added TBSCl (3.3 g, 22 mmol) portionwise under 0 °C. The solution was warmed to 50 °C and stirred for 3 h then cooled to room temperature. The solution was diluted with MTBE (12.0 mL) and quenched with H_2O (6.0 mL) under 20 °C. Aqueous layer was separated and organic layer was washed with H_2O (6.0 mL) and aq. 20% NaCl solution (6.0 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and dried *in vacuo* to give crude **18** as white powder (5.45 g, 110%). To a solution of crude **18** (1.0 g) in MeOH (30 mL) and H_2O (3 mL) was added the seed **18** (1.0 mg) at 10 °C and stirred for 4.5 h. The resulting slurry was cooled to 5 °C at the speed of 20 °C /h and stirred for 1 h. To the resulting slurry was slowly added ice-cooled H_2O (5 mL) for 10 min and stirred for another 1 h at 5 °C. The resulting slurry was filtered off and washed with ice-cooled H_2O (10 mL) and dried *in vacuo* at 40 °C to give **18** as a white powder (819 mg, 91.4% in 2 steps from diol **17**, 97.0 HPLC area %). R_f 0.49 (EtOAc/*n*-hexane, 1/3); Mp 68−70 °C; $[\alpha]^{20}_D$ −20.2(c 1.08, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 1H), 7.15 (m, 2H), 7.07 (m, 1H), 5.52 (ddd, 1H, J = 15.5, 5.7, 1.0 Hz), 5.33 (ddd, 1H, J = 15.5, 7.7, 1.1 Hz), 4.91 (td, 1H, J = 7.1, 2.2 Hz), 4.42 (s, 2H), 4.23 (m, 1H), 3.93 (q, 1H, J = 5.2 Hz), 3.38 (s, 3H), 2.73 (m, 3H), 2.56 (m, 1H), 2.43 (m, 2H), 2.17 (ddd, 1H, J = 14.8, 7.0, 5.7 Hz), 1.95 (m, 1H), 0.87 (s, 9H), 0.83 (s, 9H), 0.04 (s, 6H), −0.12 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.1, 138.7, 138.1, 135.0, 129.3, 129.2 (2C), 128.2, 125.7, 83.6, 78.2, 74.8, 74.4, 58.3, 56.8, 45.4, 42.4, 40.7, 35.2, 25.95 (3C), 25.87 (3C), 18.3, 18.1, −4.5, −4.6, −4.7, −5.0; IR (KBr) 2929, 2856, 1752, 1250, 1165, 1117, 836, 777 cm^{-1}; Mass (ESI, Pos., 20 V) m/z 583 (M + Na); HRMS (ESI) Calcd for $C_{31}H_{52}O_5Si_2$+Na^+ 583.3246; Found: 583.3265; Anal. Calcd for $C_{31}H_{52}O_5Si_2$ C, 66.38; H, 9.34; Si, 10.01; Found: C, 66.02; H, 9.38; Si, 9.93; HPLC: YMC-Pack-ODS-A-302; MeCN/H_2O = 40/60 (0−5 min) → 2%/min (5−30 min) → 90/10 (30−45 min); detection: 210 nm; flow rate: 1.0 mL/min; retention time of **18** was 34.5 min.

(1*S*,2*R*,3*R*,4*R*)-4-{[Dimethyl(2-methyl-2-propanyl)silyl]oxy}-3-{(1*E*,3*S*)-3-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-2-(2-hydroxyethyl)cyclopentanol 19. To a slurry $LiBH_4$ (102 mg, 4.70 mmol) in THF (8.3 mL) was added solution of **18** (2.78 g, 4.95 mmol) in THF (8.3 mL) at 0 °C and then stirred at 35 °C for 3 h. The reaction mixture was diluted with EtOAc (14 mL) and quenched with aq. 20 wt% NH_4Cl solution (8.3 mL) at 0 °C. Aqueous layer was separated and organic layer was washed with aq. 20% NaCl solution (5.6 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and dried *in vacuo* to give **19** as white pale yellow oil (2.84 g, 102%. 90.8% de, 98.7 area%) without further purification. R_f 0.34 (EtOAc/*n*-hexane, 1/1); $[\alpha]^{20}_D$ −5.4 (c 1.00, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.24 (m, 1H), 7.15 (m, 2H), 7.08 (m, 1H), 5.47 (dd, 1H, J = 15.2, 6.2 Hz), 5.30 (ddd, 1H, J = 15.3, 9.0, 0.82 Hz),4.42 (s, 2H), 4.25 (m, 1H), 4.17 (m, 1H), 3.96 (m, 1H), 3.66 (m, 1H), 3.57 (m, 1H), 3.39 (s, 3 H), 2.80 (dd, 1H, J = 13.4, 7.1), 2.72 (dd, 1H, J = 13.3, 6.1 Hz), 2.24 (m, 1H), 1.91 (dt, 1H, J = 14.0, 5.0 Hz), 1.81 (m, 2H), 1.54 (m, 2H), 0.87 (s, 9H), 0.84 (s, 9H), 0.05 (m, 6H), −0.08 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.9, 137.9, 133.8, 131.5, 129.3 (2C), 128.2, 125.7, 79.6, 74.9, 74.9, 74.5, 61.9, 58.3, 56.6, 49.2, 45.5, 42.9, 31.6, 26.0 (3C), 25.9 (3C), 18.3, 18.0, −4.41, −4.44, −4.7, −5.0; IR (KBr) 3383, 2953, 2929, 2856, 1741, 1472, 1254, 1105, 837, 776 cm^{-1}; Mass (ESI, Pos., 20 V) m/z 587 (M + Na); HRMS (ESI) Calcd for $C_{31}H_{56}O_5Si_2$+Na^+ 587.3559; Found: 583.3586; Anal. Calcd for $C_{31}H_{56}O_5Si_2$: C, 65.91; H, 9.99; Si, 9.94; Found: C, 65.72; H, 10.24; Si, 9.54; HPLC conditions: YMC-Pack-ODS-A-302; MeCN/H_2O = 75/25; detection: 210 nm; flow rate: 1.0 mL/min; retention time of **19** was 12.6 min, and that of 15-β was 13.3 min.

Methyl 4-({2-[(1*R*,2*R*,3*R*,5*S*)-3-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-2-{(1*E*,3*S*)-3-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-hydroxycyclopentyl]ethyl}sulfanyl)butanoate 20. To a solution of γ-thiobutyrolactone (2.73 g, 26.8 mmol) in MeOH (5.5 mL) was added Cs_2CO_3 (873 mg, 2.68 mmol) under Ar and stirred for 2 h at 50 °C. The resulting solution was cooled to rt, and then the solution was diluted with DMA (18.2 mL) to give methyl 4-mercaptobutanoate DMA solution.

To a solution of MsCl (0.83 mL, 11 mmol) in THF (30.2 mL) was added a mixed solution of diisopropylethylamine (2.6 mL, 15 mmol) and **19** (5.04 g, 8.92 mmol) in THF (30.4 mL) at −20 °C and stirred for 30 min. To a slurry was added MeOH (0.14 mL, 3.6 mmol) at −20 °C and stirred for 30 min. To a slurry was added TMSCl (1.7 mL, 13 mmol) at −20 °C and stirred for 30 min. The slurry was warmed to 0 °C and Cs_2CO_3 (17.4 g, 53.5 mmol) was added and stirred for 10 min. To the slurry was added a solution of methyl 4-mercaptobutanoate in DMA at 0 °C and warmed to 40 °C and stirred for another 2.5 h. To a slurry was added MeOH (10 mL) at rt and stirred for 16 h. The reaction mixture was diluted with MTBE/EtOAc = 2/1 (101 mL), then quenched with H_2O (50 mL) under 15 °C. Aqueous layer was separated and extracted with MTBE/EtOAc = 2/1 (50 mL) and the combined organic layers was washed with H_2O (25 mL), aq. 20% NaCl solution (25 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (BW-235S, 169 g, Toluene:EtOAc = 10:1) to give **20** as a colorless oil (4.75 g, 78.2%, 93.2% de, 97.3 area%). R_f 0.40 (EtOAc/*n*-hexane, 1/4); $[\alpha]^{20}_D$ +11.9 (c 1.02, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.24 (t, 1H, J = 7.6 Hz), 7.15 (d, 1H, J = 7.7 Hz), 7.13 (s, 1H), 7.07 (d, 1H, J = 7.5 Hz), 5.49 (dd, 1H, J = 15.4, 5.7 Hz), 5.35 (ddd, 1H, J = 15.3, 8.9, 0.92 Hz), 4.42 (s, 2H), 4.22 (q, 1H, J = 6.0), 4.12 (m, 1H), 3.98 (m, 1H), 3.65 (s, 3H), 3.37 (s, 3 H), 2.73 (d, 2H, J = 6.6), 2.54 (m, 4H), 2.42 (t, 2H, J = 7.3), 2.22 (m, 1H), 1.88 (m, 5H), 1.59 (m, 2H), 0.86 (s, 9H), 0.82 (s, 9H), 0.04 (m, 6H), −0.13 (s, 3H), −0.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.6, 138.9, 138.0, 133.7, 131.2, 129.4, 129.3, 128.2, 125.6, 80.1, 74.8, 74.6, 74.5, 58.2, 56.9, 51.7, 50.6, 45.6, 43.0, 32.9, 31.3, 30.6, 29.0, 26.0 (3C), 25.9 (3C), 24.8, 18.3, 18.0, −4.4, −4.5, −4.7, −5.1; IR (KBr) 3513, 2928, 2856, 1254, 1104, 971, 837, 776 cm^{-1}; Mass (ESI, Pos., 20 V) m/z 703 (M + Na); HRMS (ESI) Calcd for $C_{36}H_{64}O_6S_1Si_2$+Na^+: 703.3854; Found: 703.3878; Anal. Calcd for $C_{36}H_{64}O_6S_1Si_2$ C, 63.43; H, 9.56; S, 4.71; Si, 8.25; Found: C, 63.48; H, 9.47; S, 4.71; Si, 8.07; HPLC conditions: YMC-Pack-C4-A-802; MeCN/H_2O = 80/20 (0−15 min) → 2%/min (15−25 min)→ 100/0 (25−35 min); detection: 210 nm; flow rate: 1.0 mL/min; retention time of **20** was 17.6 min, and that of 15-β was 16.7 min.

Methyl 4-({2-[(1*R*,2*R*,3*R*)-3-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-2-{(1*E*,3*S*)-3-{[dimethyl(2-methyl-2-propanyl)silyl]oxy}-4-[3-(methoxymethyl)phenyl]-1-buten-1-yl}-5-oxocyclopentyl]ethyl}sulfanyl)butanoate 21. To a stirred solution of **20** (2.0 g, 2.9 mmol) and diisopropylethylamine (2.23 g, 17.3 mmol) in EtOAc (20 mL) was added a solution of SO_3·Py (1.38 g, 8.64 mmol) in DMSO (10 mL) slowly at a temperature below 10 °C under Ar. After

stirring for 10 min, the reaction mixture was diluted with MTBE (20 mL) and slowly quenched with H_2O (40 mL). The mixture was washed ice-cooled 1 M HCl solution (30 mL) and the aqueous layer was extracted with MTBE (20 mL). The combined organic layers was washed with H_2O (20 mL), aq. 9% $NaHCO_3$ solution (20 mL), aq. 20% NaCl solution (20 mL), and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (BW-235S, 40 g, EtOAc/*n*-hexane, 1/4) to give **21** as a colorless oil (1.81 g, 92.5%, 97.7 HPLC area %). R_f 0.50 (EtOAc/*n*-hexane, 4/1); $[\alpha]^{20}_D$ −37.3 (c 0.42, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, 1H, J = 7.6 Hz), 7.16 (d, 1H, J = 7.7 Hz), 7.14 (s, 1H), 7.08 (d, 1H, J = 7.3 Hz,), 5.66 (dd, 1H, J = 15.4, 4.9 Hz), 5.54 (ddd, 1H, J = 15.3, 8.1, 1.2 Hz), 4.42 (s, 2H), 4.28 (m, 1H), 4.04 (q, 1H, J = 7.6 Hz), 3.66 (s, 3H), 3.37 (s, 3 H), 2.75 (m, 2H), 2.60 (m, 2H), 2.50 (t, 2H, J = 7.1 Hz), 2.50 (m, 1H), 2.41 (t, 2H, J = 7.3 Hz), 2.42 (m, 1H), 2.21 (dd, 1H, J = 18.4, 8.0 Hz), 2.06 (m, 1H), 1.81 (m, 4H), 0.88 (s, 9H), 0.83 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), −0.11 (s, 3H), −0.28 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.3, 173.4, 138.7, 135.9, 129.1 (2C), 128.9, 128.1, 125.5, 74.6, 73.8, 73.1, 58.0, 53.4, 52.3, 51.5, 47.2, 45.3, 32.7, 30.9, 29.1, 27.9, 25.82 (3C), 25.78 (3C), 24.5, 18.1, 18.0, −4.5 (2C), −5.2, −5.3; IR (Liquid film) 2952, 2928, 2856, 1741, 1471, 1253, 1112, 883, 837, 776 cm^{-1}; Mass (ESI, Pos., 20 V) m/z 701 (M + Na); HRMS (ESI) Calcd for $C_{36}H_{62}O_6S_1Si_2$+Na^+: 701.3698, Found: 701.3730; Anal. Calcd for $C_{36}H_{62}O_6S_1Si_2$: C, 63.67; H, 9.20; S, 4.72; Si, 8.27; Found: C, 63.68; H, 9.37; S, 4.71; Si, 8.17; HPLC conditions: DAISOPAK SP-200−5−C4-P, MeCN/H_2O = 70/30, detection: 210 nm, flow rate: 1.0 mL/min, retention time of **21** was 16.4 min.

16-(3-Methoxymethyl)phenyl-ω-tetranor-5-thiaPGE$_1$ methyl ester ONO-4819. To a stirred solution of **21** (2.63 g, 3.87 mmol) in MeCN (25 mL) was added a solution of aq. 25% H_2SiF_6 solution (2.3 g, 4.0 mmol) at a temperature around 10 °C under Ar. After stirring for 3.5 h, the reaction mixture was diluted with EtOAc (13 mL) and quenched with a mixture of K_3PO_4 (3.29 g, 15.5 mmol) and KH_2PO_4 (1.05 g, 7.74 mmol) in H_2O (26 mL). To a solution was added KC-Flock (920 mg) and filtered off. The aqueous layer was separated and extracted with EtOAc (13 mL). The combined organic layers was washed with aq. 20% NaCl solution (26 mL), and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (60N, 131.5 g, EtOAc→EtOAc/MeOH = 50/1) to give **ONO-4819** as a colorless oil (1.55 g, 89.0%, > 99.99% de, 99.8 HPLC area%, assay 98.9% by HPLC absolute calibration method). R_f 0.44 (MeOH/$CHCl_3$, 1/9); $[\alpha]^{20}_D$-42 (c1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.10 (m, 4H), 5.75 (dd, 1H, J = 5.6, 15.2 Hz), 5.53 (dd, 1H, J = 8.8, 15.2 Hz), 4.43 (s, 3H), 4.45−4.35 (m, 1H), 3.96 (q, 1H, J = 8.0 Hz), 3.67 (s, 3H), 3.42 (s, 3 H), 2.95−2.75 (m, 2H), 2.80−2.00 (m, 10H), 2.00−1.60 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ214.5, 173.7, 138.2, 137.9, 135.8, 132.3, 129.1, 129.0, 128.5, 126.1, 74.8, 73.5, 71.6, 58.4, 54.7, 52.7, 51.7, 45.7, 43.9, 32.9, 30.7, 29.1, 27.4, 24.6; IR (neat) 2952, 2928, 2856, 1741, 1471, 1253, 1112, 883, 837, 776 cm^{-1}; Mass (FAB, Pos) m/z 451 (M + H); HPLC conditions: YMC-Pack-ODS-A-302, gradient A: H_2O/MeOH = 9/1, B: MeCN, A/B = 80:20 (0 min) → 55/45 (80 min), detection: 210 nm, flow rate: 1.0 mL/min, retention time of **ONO-4819** was 31 min, and that of 15-β was 30 min.

3-Bromobenzylmethylether 46. Under an atmosphere of argon gas, to a solution of **45** (3.56 kg, 19.0 mol) in THF (35.5 L) was added KOH (3.77 kg, 57.1 mol) and $(MeO)_2SO_2$ (3.60 kg, 28.1 mol) under the temperature 30 °C. The reaction mixture was warmed and refluxed for 3 h, then cooled to rt. The solvent of reaction mixture was removed under reduced pressure. To the residue was added water (32 L) and MTBE (32 L) and aqueous layer was separated. The organic layer was washed water (5 L), aq. 20% NaCl solution (8 L) and dried over anhydrous $MgSO_4$ (2.20 kg). The solvent was removed by evaporation to give **46** as yellow oil (3.53 kg, 92.2%) without further purification. R_f 0.80 (EtOAc/*n*-hexane, 1/4); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55−7.36 (m, 2H), 7.28−7.12 (m, 1H), 4.41 (s, 2H), 3.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$); δ 140.5, 130.6, 130.5, 129.9, 126.0, 122.5, 73.8, 58.3; Mass (FAB, Pos) m/z 202 (M+H); IR (neat) 2986, 2927, 2821, 1571, 1471, 1426, 1378, 1197, 1108, 777 cm^{-1}.

3-Methoxymethylphenylacetic acid 43. Under an atmosphere of argon gas, to a mixture of NaH (42.2 g, 1.08 mol) and THF (350 mL) was added ethylcyanoacetate (62.0 g, 0.538 mol) in THF (50 mL) at the temperature below 15 °C. After stirring for 5 min, to the slurry was added **46** (90.0 g, 0.448 mol) in THF (50 mL) and $Pd(PPh_3)_4$ (5.2 g, 4.4 mol) successively at the temperature below 25 °C, then refluxed for 6 h. The mixture was cooled to under 30 °C, EtOH (70 mL) was added to quench the reaction, and the resulted mixture was stirred for 20 min at the temperature around 25 °C. The solvent was removed under reduced pressure until removed solvent was about 4 v/w (ca. 360 mL) of **46**. To the residue was added aq 2 M NaOH. solution (600 mL) and MTBE (650 mL) and an aqueous layer was separated, and then an organic layer was washed with MTBE (650 mL). To the combined aqueous layers which contained **47** was slowly added NaOH (72 g, 18 mol) at the temperature under 50 °C. The mixture was heated and the solvent was removed under atmospheric pressure until the inert temperature reached to 100 °C, and then stirred for 4 h at 100 °C. The solution was cooled to under 15 °C and water (400 mL) was added to the resulted residue. To the solution was added 6 M HCl solution (800 mL) to control the pH around 2−3. EtOAc (900 mL) was added and the aqueous layer was separated. An aqueous layer was extracted with EtOAc (400 mL) and the combined organic layers was washed with aq. 20% NaCl solution (360 mL) twice and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation give **43** as yellow oil (76.2 g, 94.4% from **46**) without further purification. R_f 0.31 (EtOAc/*n*-hexane, 1/2); ^{1}H NMR (200 MHz, $CDCl_3$) δ.7.38−7.18 (m, 4H), 4.45 (s, 2H), 3.65 (s, 2H), 3.39 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.4, 138.4, 133.4, 128.7 (2C), 126.6 (2C), 74.4, 58.1, 40.9; Mass (ESI, Neg) m/z 179 (M - H); IR (neat) 2934, 1709, 1449, 1411, 1383, 1194, 1089, 917, 769, 708 cm^{-1}.

N-Methoxy-N-methyl-(3-methoxymethylphenyl)acetic acid amide 44. Under atmosphere of argon gas, to a solution of **43** (2.95 kg, 16.4 mol) in MeCN (20 L) was added *N*, *O*-dimethylhydroxylamine hydrochloride (2.40 kg, 24.6 mol) and 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide monohydrochloride (EDC) (1.08 kg, 21.3 mol) successively.Thereto, Et_3N (2.49 kg, 24.6 mol) in MeCN (4 L) was added at the temperature below 10 °C and stirred for 1 h around 15−30 °C. The solvent was removed by evaporation, and to the resulting residue was added 1 M HCl solution (13.1 L) and EtOAc (14 L) and the aqueous layer was separated. The aqueous layer was extracted with EtOAc (10 L) twice and the combined organic layers was washed aq. 20% NaCl solution (10 L), aq. 9% $NaHCO_3$ solution (9 L) and aq. 20% NaCl solution (10 L) successively. The organic layer was dried over anhydrous $MgSO_4$ (3.00 kg) and concentrated under reduced pressure. Azeotropic distillation with toluene (10 L) under reduced pressure to obtain **44** as brown oil (3.40 kg, 93.0%). R_f 0.55 (EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ.7.36−7.18 (m, 4H), 4.44 (s, 2H), 3.78 (s, 2H), 3.61 (s, 3H), 3.38 (s, 3H), 3.20 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3, 138.5, 135.1, 128.73, 128.70, 128.6, 126.2, 74.7, 61.4, 58.2, 39.4, 32.4; Mass (ESI, Pos) m/z 246 (M + Na); IR (neat) 2934, 2896, 2822, 1664, 1448, 1382, 1193, 1107, 1006, 771, 699 cm^{-1}.

Dimethyl-3-(3-methoxymethylphenyl)-2-oxopropylphosphonate 3. Under atmosphere of argon gas, a solution of dimethyl methylphosphonate (2.67 kg, 21.5 mol) in toluene (55 L) was cooled to

−60 °C. Thereto, *n*-butyllithium (1.58 M *n*-hexane solution, 13.1 L, 20.0 mol) was added at the temperature below −50 °C and stirred for 30 min at 60 °C. To a mixture was added **44** (3.20 kg, 14.3 mol) in toluene (15 L) at the temperature below −60 °C and stirred for 2 h. To the reaction mixture was added acetic acid (1.20 kg, 20.1 mol) and warmed to 0 °C. To the solution was added ice-cooled aq 1 M NaOH solution (36.2 L) and MTBE (30 L), and the organic layer was separated. To the aqueous layer was added 6 M HCl solution (9.6 L) to control the pH around 3−4. In addition, EtOAc (24 L) was added, and the aqueous layer was separated. The aqueous layer was extracted with EtOAc (13 L) twice. To the aqueous solution were added NaCl (10 kg) and EtOAc (12 L), and the aqueous layer was separated. The combined organic layers was washed with aq 20% NaCl solution (10 L) twice, aq 9% $NaHCO_3$ solution (5 L), and aq 20% NaCl solution (7 L) successively and dried over anhydrous $MgSO_4$ (3.00 kg). The solution was concentrated, and azeotropic distillation with THF (10 L) under reduced pressure provided **3** as a brown oil (3.12 kg, 76.2%): R_f 0.22 (EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ.7.38−7.11 (m, 4H), 4.45 (s, 2H), 3.90 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.40 (s, 3H), 3.11 (d, 2H, J = 23 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.3, 138.8, 133.3, 128.82, 128.77, 126.6, 74.4, 58.2, 53.2, 53.0, 50.7, 41.5, 39.0; MS (ESI, Pos) m/z 287 (M + H); IR (liquid film) 3482, 2956, 2928, 2855, 2824, 1720, 1450, 1259, 1187, 1032, 816 cm^{-1}.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.