

An Efficient Asymmetric Synthesis of Prostaglandin E₁Ana Rodríguez,^[a] Miguel Nomen,^{[a][†]} Bernd Werner Spur,^{*[a]} and Jean-Jacques Godfroid^[b]**Keywords:** Prostaglandins / Asymmetric synthesis / In situ inversion / CBS reduction / Cuprates

An asymmetric total synthesis of Prostaglandin E₁ (**5**) has been achieved in a two-component coupling process. The chiral hydroxycyclopentenone **6** was readily available from furan with 96% ee. The key reaction step was a kinetic enzymatic resolution followed by an in situ inversion. A catalytic asymmetric reduction of the γ -iodo vinyl ketone **19**

with the Corey CBS catalyst gave the ω -side chain **7** with >96% ee. Conjugate addition using the reaction with dilitiocyancuprate followed by mild cleavage of the silyl protective groups and enzymatic hydrolysis of the methyl ester **22** gave (–)-PGE₁ **5** in high yield.

Introduction

Prostaglandins belong to the family of polyoxygenated fatty acids that are produced enzymatically by cyclooxygenase type I (COX-1) and cyclooxygenase type II (COX-2).^[1] Several natural prostaglandins and analogs are used as drugs.^[2] In recent years new indications, especially for the E and F types, have been clinically introduced. Several studies on asthmatic subjects have shown a highly protective effect of inhaled prostaglandins of the E-type on various challenges, e.g. allergen, exercise, aspirin, etc.^[3] Termination of pregnancy (misoprostol),^[4] treatment of male impotency (prostaglandin E₁)^[5] and treatment of glaucoma (lantanoprost)^[6] are other remarkable examples.

Recently it was reported that isomeric prostaglandins (isoprostanes) are formed in vivo by a nonenzymatic, free-radical-catalyzed peroxidation of polyunsaturated fatty acids.^[7] These molecules serve as markers of oxidative stress in degenerative diseases e.g. arteriosclerosis and Alzheimer's disease.^[8]

As part of our ongoing interest in cyclooxygenase and lipoxygenase products we required larger amounts of prostaglandin E₁ (**5**). Our goal was to develop an asymmetric synthetic route from simple prochiral starting materials that could easily be scaled up.

The first general synthetic route to all natural prostaglandins was developed by Corey et al. In this classical approach both side chains were introduced by Wittig and Wittig–Horner reactions (Figure 1).^[9] The key intermediate, the “Corey lactone”, is still the basis for the industrial synthesis of prostaglandins.^[10] A great effort has been made over the years to improve the original synthesis. An asymmetric Diels–Alder reaction using phenylmenthol as a chiral auxiliary to build up the bicyclo[2.2.1]heptene system has been reported by Corey et al.^[11] Later, this group de-

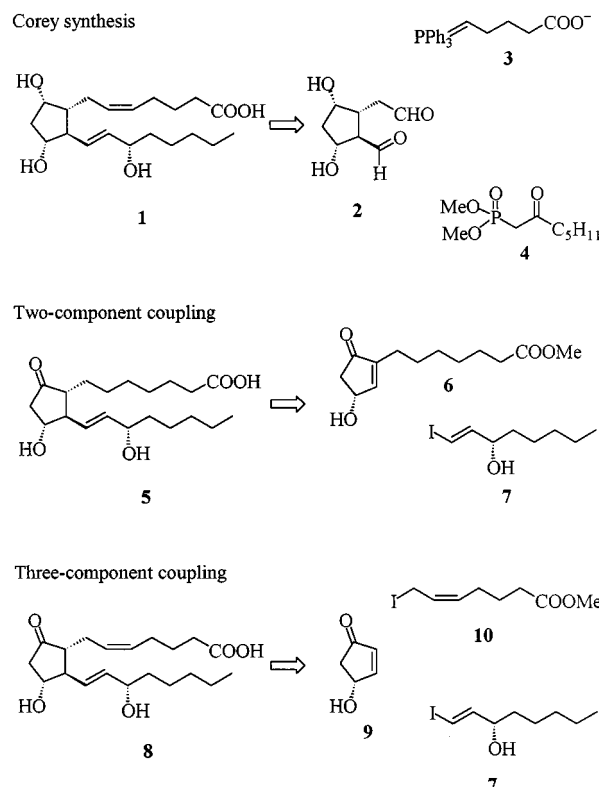


Figure 1. Retrosynthetic analysis of the three major routes to prostaglandins

scribed a catalytic enantioselective Diels–Alder reaction with a chiral Lewis acid catalyst achieving the [4+2] adduct with >95% ee.^[12] Another important challenge in this route was the control of the C-15 stereochemistry which still attracts much attention today.^[13] Several reductions of the α,β -unsaturated ketone intermediate in Corey's synthesis have been reported, e.g. with bulky trialkylborohydrides at -100°C (88% ee),^[14] CBS at room temperature (93% ee),^[15] Yamamoto's diisobutylaluminum-2,6-di-*tert*-butyl-4-methylphenoxide complex at -78°C (85% ee)^[16] and Noyori's BINAL-H catalyst -80°C (99% ee).^[17] The drawbacks of some of these methods are very low temperatures or high costs of the reagents (e.g. BINOL) when used in

^[a] Department of Cell Biology, University of Medicine and Dentistry of New Jersey, SOM 2 Medical Center Drive, Stratford, 08084 NJ, USA
Fax: (internat.) + 1-856/983-4953
E-mail: spurbw@umdnj.edu

^[b] Laboratoire de Pharmacochimie Moléculaire, Université Paris 7 Paris 75251, France

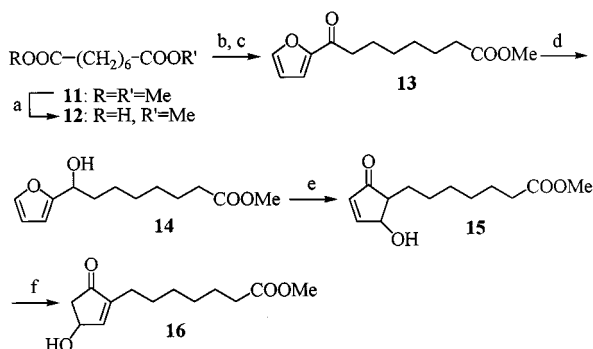
^[†] Deceased September 26, 1997

excess. Specific solutions have been found for several prostaglandins: Yamamoto's reduction gave 100% *ee* in dimoxaprost^[18] and the Meerwein–Ponndorf–Verley reduction gave 98% *ee* in cloprostenol.^[19]

Although PGE₁ has been prepared from PGF_{2α} the additional reaction steps, combined with the problem of over-reduction to impurities of undesired biological activities, led us to consider another approach.^[20] The two-component coupling strategy, first reported by the Syntex group,^[21] has mainly been used for the synthesis of racemic prostaglandins of the E-type, such as misoprostol,^[22] due to the unavailability of a convergent way to obtain the chiral building block **6**.^[23] Later on Babiak et al. reported the enzymatic resolution of hydroxycyclopentenones, including **16**, which makes this process attractive for the synthesis of the natural prostaglandins (Figure 1).^[24] The most elegant synthesis, the "three-component coupling", was developed by Noyori et al. (see Figure 1).^[25] An efficient synthesis of the chiral hydroxycyclopentenone **9** has been described by Jacobsen et al. using the kinetic resolution of epoxy–cyclopentanone with the (Cr)Salen-catalyst and (CH₃)₃SiN₃.^[26] Unfortunately for the prostaglandins of the one series, especially PGE₁, Noyori's approach was not of practical synthetic use due to the low reactivity of a suitable α-side chain or its instability under the reaction conditions required.^[27] Johnson et al. have reported a new procedure applying a modified Suzuki coupling which, in fact, produces the intermediate used in the two-component coupling.^[28]

Results and Discussion

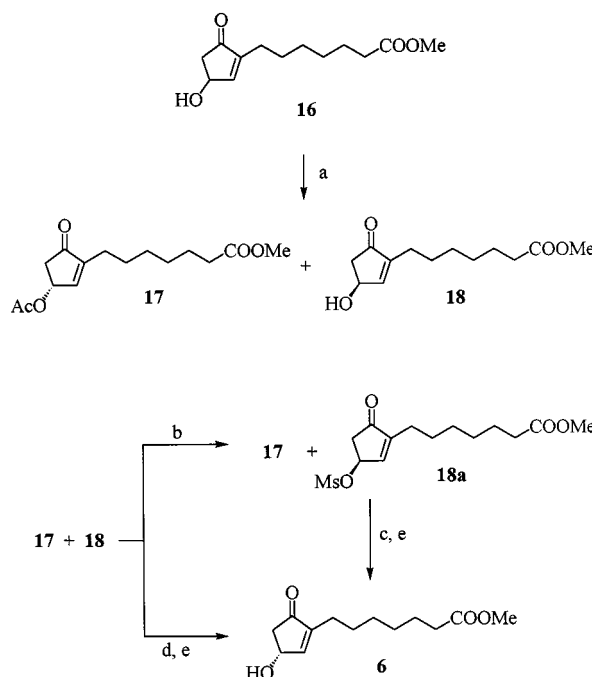
In this paper we report a convergent synthesis of (–)-prostaglandin E₁ starting from prochiral intermediates **16** and **19**. After simple transformations to the chiral key intermediates **6** and **7**, **5** was readily available from the two-component coupling. The synthesis of **16** from commercially available furan and suberic acid is outlined in Scheme 1.



Scheme 1. Synthesis of **16** from dimethyl suberate (**11**) and furan

Suberic acid was converted into its half ester **12** in two steps. Esterification using our recently developed method at

room temperature produced the diester **11** in quantitative yield.^[29] Enzymatic cleavage of **11** with the inexpensive porcine pancreatic lipase (PPL, Sigma) gave **12** in 85% yield.^[30] Compound **12** was converted into the mixed anhydride with chloroacetyl chloride in CCl₄ at 0°C in the presence of 1 equivalent of Et₃N.^[31] The precipitated Et₃N·HCl was removed by filtration and the crude mixed anhydride was reacted with furan at room temperature in the presence of a catalytic amount of BF₃·Et₂O.^[32] Simple distillation afforded the ketoester **13** in 67% yield. NaBH₄ reduction in MeOH at 0°C gave the hydroxyester **14** in 95% yield. The use of EtOH instead of MeOH resulted in substantial amounts of the corresponding hydroxyethyl ester due to a transesterification catalyzed by borates. Crude **14**, after evaporation of MeOH, was used directly in the following rearrangement step to give **15**. The reaction was best carried out at reflux temperature in dioxane/H₂O with ZnCl₂ as catalyst producing a mixture of the hydroxycyclopentenone **15** and **16**.^[33] Treatment of this mixture with Et₃N and a catalytic amount of chloral in toluene, according to Stork,^[34] afforded crystalline **16** in 72% yield.



Scheme 2. Kinetic enzymatic resolution of **16** and in situ inversion to (*R*)-**6**

As described by Babiak et al. the racemic **16** could be resolved enzymatically with vinyl acetate and PPL at room temperature to give 46% of the (*R*)-acetate **17** and 41% of the (*S*)-hydroxy **18** both with 98% *ee*.^[24] The authors reported that chromatography is a necessary purification process since failure to remove the acetate **17** from the alcohol **18** quantitatively led to racemization.^[24b] Isolated **18** has been converted into **6** using the Mitsunobu inversion.^[35]

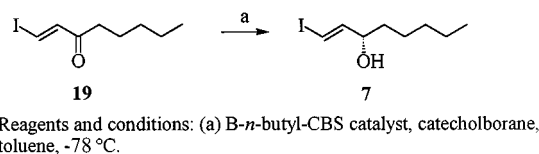
Table 1. In situ inversion of **18** in the presence of **17**

Entry	Substrate	Method	Conditions of Inversion	Solvent	ee [%] ^[b]
1	17 + 18	A	Mitsunobu	THF	96
2	17 + 18 ^[a]	B (B')	NaOAc	Dioxane/H ₂ O	84(94) ^[c]
3	17 + 18 ^[a]	C	CsOAc	CH ₃ CN	91
4	17 + 18 ^[a]	D	CsOAc/18-crown-6	CH ₃ CN	92
5	17 + 18 ^[a]	E	CsF/AcOH	DMF	91
6	17 + 18 ^[a]	F	NaOAc/CsF	Dioxane/H ₂ O	81
7	17 + 18 ^[a]	G	Guanidine	CH ₃ OH	80

^[a] **18** was converted in situ into the mesylate **18a** prior to inversion. — ^[b] Determined by chiral HPLC of **6** using Chiracel OD or OB columns. — ^[c] The crude mixture of **17** and **6** from the inversion reaction was resubmitted to PPL, the remaining **18** was removed by complexation with anhydrous LiBr.

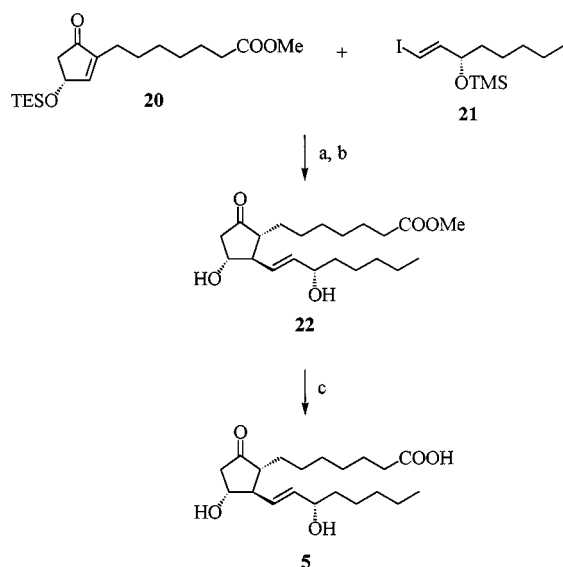
The most practical process would directly use the crude mixture from the enzymatic reaction for the inversion of the (*S*)-stereocenter in **18** to the correct (*R*)-configuration (Scheme 2). Only a few examples have been described in the literature, with *ee* values ranging from 63% to 97%, but they require reaction conditions which are unsuitable for our substrate.^[36] For example, Danda, and Faber, have used drastic conditions (fuming nitric acid followed by enzymatic hydrolysis or hydrolysis at reflux), which interferes with the functionality of our substrate.^[36d,36e] Theil and Ikegami used CsOAc in toluene or benzene at reflux in the presence of 18-crown-6 for the inversion.^[36f,37a] The addition of 18-crown-6 was necessary, as reported by Ikegami, to suppress olefin formation.^[37a] The use of CsF in DMF in the presence of an acid was described by Otera as a practical method for the inversion of secondary mesylates at elevated temperatures.^[37b] Due to the sensitive nature of our substrate the inversion was conducted at low temperature and only mild reaction conditions were used. Therefore, we first investigated the Mitsunobu reaction for the in situ inversion of **18** in the presence of **17**, and obtained **6** after hydrolysis with guanidine in 76% isolated yield and with 96% *ee* as determined by chiral HPLC (Table 1, entry 1, method A). One of the major drawbacks of the Mitsunobu reaction is the difficulty of removing the redox by-products triphenylphosphane oxide and bis(ethoxycarbonyl)hydrazine, which becomes a major concern in large-scale applications. Consequently we tested various sulfonates for the S_N2 reaction that produce water-soluble by-products which can easily be removed.^[37] The mesylate is formed rapidly in high yield whereas the tosylate is formed only sluggishly. Accordingly, the mixture of **17** and **18** was treated with 57 mol-% of methanesulfonyl chloride in the presence of 62 mol-% of Et₃N. Using several conditions for the inversion reaction (Table 1, entries 2–7, method B–G), and after guanidine cleavage, **6** was obtained in *ee* values ranging from 80–92%. When the crude mixture of **17** and **6** (Table 1, entry 2, method B') was re-submitted to PPL in vinyl acetate the initial 84% *ee* value was improved to 94% *ee*. The small amount of remaining **18** was removed by complexation with LiBr prior to hydrolysis.^[38] Silylation of **6** produced the key intermediate **20** in 88% yield after distillation.

In order to introduce concurrently the correct stereocenter at C-15 we required the optically active side chain **7**.

Scheme 3. Catalytic asymmetric CBS reduction of the β-iodovinyl ketone **19**

Approaches using microbiological reduction (80% *ee*, 12% yield),^[39] enzymatic resolution (50% *ee*, 31% yield)^[40] and the Sharpless kinetic resolution (99% *ee*, 45% yield)^[41] have been described. Noyori et al. applied the BINAL catalyst at -80 °C to reduce the 1-iodo-1-(*E*)-octen-3-one (**19**) and obtained **7** with 94–97% *ee* and 96% yield. Three equivalents of the chiral reagent had to be used and chromatographic separation was required in order to remove and recover the BINOL ligand.^[42] Corey et al. have described the reduction of **19** by means of chiral oxazaborolidines, and obtained the allyl alcohol **7** with 86% *ee* in 95% yield.^[43] In earlier experiments we realized that catecholborane reacted at low temperatures with **19**. In order to avoid uncatalyzed reduction we examined the extremely slow addition of catecholborane (over 12 hours) to the ketone **19** at -78 °C in the presence of 5% CBS catalyst. Under these conditions we obtained the allyl alcohol **7** in 95% isolated yield and >96% *ee* as determined by chiral HPLC and Mosher ester analysis. On a large scale the amount of catalyst was successfully reduced to 1% without loss of optical purity. Simple aqueous work-up afforded the product in almost pure form. The best results were obtained at low temperature and with the use of the B-*n*-butyl catalyst. The B-methyl catalyst gave substantial less optical induction and at higher temperatures the *ee* value dropped due to noncatalyzed reduction. Standard silylation (Me₃SiCl, imidazole, Et₃N in DMF) produces the silyl ether **21** in high yield.^[44]

The two-component coupling of the chiral hydroxycyclopentenone **20** with **21** provided the 1,4-addition product.^[45] Mild desilylation produced the crystalline PGE₁ methyl ester (**22**) in 85% yield. The final enzymatic hydrolysis with PPL (Sigma) at pH 7 produced the highly crystalline PGE₁ (**5**) as white needles. Recrystallization from hot EtOAc gave PGE₁ that was identical in all aspects (TLC, HPLC, m.p., [α]_D, FT-IR, API-ES/MS, ¹H-, ¹³C NMR spectroscopy) with an authentic sample (Upjohn). The purity was deter-



Reagents and conditions: (a) *n*-BuLi, CuCN, MeLi, Et₂O, -78 °C; (b) PPTS, acetone/H₂O; (c) Lipase (PPL), NaCl, CaCl₂, H₂O/THF, NaOH

Scheme 4. Synthesis of PGE₁ (**5**) by the two component coupling of **20** and **21**

mined to be >99% as assayed by HPLC, HPLC/API-ES/MS and NMR. The C-15 (*S*)-purity was >99.7% as determined by GC analysis.^[46]

Conclusion

In conclusion a stereoselective synthesis of PGE₁ by a two-component coupling has been achieved. The two chiral components **20** and **21** were obtained by a kinetic enzymatic resolution combined with an in situ inversion, and by a catalytic asymmetric reduction, respectively. The transformation of PGE₁ into PGA₁,^[47] PGB₁,^[48] PGC₁,^[49] PGD₁,^[50] PGF₁^[51] is well described in the literature. In addition epimerization of the C-8 center could be accomplished with KOAc in MeOH giving easy access to the 8-iso-PGs of the one series.^[52] These nonenzymatic free-radical-induced peroxidation products of polyunsaturated fatty acids are currently of interest due to their unknown biological properties.^[53]

Experimental Section

General Remarks: All reactions that were moisture- and air-sensitive were carried out in flame-dried glassware and under an argon atmosphere. – The progress of the reactions was checked by thin layer chromatography (TLC) on E. Merck silica gel 60F glass plates (0.25 mm). The spots were visualized with UV light, followed by heat staining with *p*-anisaldehyde in ethanol/sulfuric acid. – Melting points were determined on a Mel-Temp capillary melting point apparatus and are uncorrected. – Silica gel 60 from EM-Science was used for flash chromatography. – HPLC analysis were performed on a Hewlett-Packard liquid chromatograph HP-1090 Series II with PV5 SDS (Solvent Delivery System) and DAD (Diode Array Detector) equipped with heated column compartment

and automatic liquid injector, or on a Waters HPLC system (M-6000A pump, M-730 Data Module integrator, U6 K Injector) and a Schoeffel SF-770 UV detector. For Chiral HPLC Chiracel OF, OD, OB columns (Daicel Chemical Ltd.) have been used. – ¹H NMR and ¹³C NMR spectra were recorded on a 300 MHz Varian Gemini 2000 Broadband High-Resolution NMR. – IR spectra were measured on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. – Optical rotation was measured on a Perkin-Elmer Polarimeter 343. – Mass Spectra were obtained using Hewlett Packard HP-59987A API-Electrospray (Atmospheric Pressure Ionization Electrospray) interface coupled to a Mass Spectrometer Hewlett Packard HP-5989B MS.

Dimethyl Suberate (11): To a solution of suberic acid (300 g, 1.72 mol) in 2,2-dimethoxypropane/MeOH 4:1 (600 mL) was added Me₃SiCl (10.9 mL, 86.0 mmol) and the mixture stirred for 24 hours at room temperature. The solvent was removed under reduced pressure affording the diester **11** in quantitative yield. – B.p. 105–110 °C/2 mm. – ¹H NMR (CDCl₃, 300 MHz): δ = 1.2–1.3 {m, 4 H, (CH₂)₂}, 1.5–1.6 (m, 4 H, CH₂–CH₂–COO), 2.2 (t, *J* = 7.3 Hz, 4 H, CH₂–COO), 3.6 (s, 6 H, CH₃O). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 24.5 (CH₂–CH₂–COO), 28.5 {CH₂–(CH₂)₂–COO}, 33.8 (CH₂–COO), 51.2 (CH₃O), 174.1 (COO).

Suberic acid monomethyl ester (12): Compound **11** (250 g, 1.24 mol) was suspended in phosphate buffer (pH 7.0, 0.05 M, 1 l). With vigorous stirring porcine pancreatic lipase (PPL, Sigma, EC 3.1.1.3, 30.0 g) was added while the pH was kept at 7 by continuous addition of 2 N NaOH (620 mL, 1.24 mol). The reaction mixture was filtered through celite/NaCl and the filtrate was washed with Et₂O (250 mL). The buffer layer was acidified to pH 2 by addition of half-concentrated HCl (≈300 mL) and extracted three times with Et₂O. The combined Et₂O layers were dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by distillation to yield **12** (198.4 g, 85%). – B.p. 130–135 °C/1 mm. – ¹H NMR (CDCl₃/[D₆]acetone, 300 MHz): δ = 1.2–1.4 {m, 4 H, (CH₂)₂}, 1.5–1.7 (m, 4 H, CH₂–CH₂–COO), 2.2 (t, *J* = 7.5 Hz, 4 H, CH₂–COO), 3.6 (s, 3 H, CH₃O). – ¹³C NMR (CDCl₃/[D₆]acetone, 300 MHz): δ = 24.2 and 24.3 (CH₂–CH₂–COO), 28.3 {2 C, CH₂–(CH₂)₂–COO}, 33.6 and 33.5 (CH₂–COO), 51.0 (CH₃O), 173.8 (COOCH₃), 177.7 (COOH).

Methyl-8-furyl-8-oxo-octanoate (13): To a solution of monoester **12** (188.2 g, 1.0 mol) and Et₃N (140.8 mL, 1.01 mol) in CCl₄ (1 l) at 0 °C was added dropwise chloroacetyl chloride (80.4 mL, 1.01 mol). When the addition was completed, the mixture was stirred at room temperature for 3 hours and then filtered to remove precipitated salts. To the filtrate was immediately added furan (109.1 mL, 1.5 mol) and BF₃·Et₂O (12.7 mL, 0.1 mol) and stirred for 12 hours. The solution was washed successively with water (150 mL), 5% Na₂CO₃ (150 mL) and water (150 mL). Drying over Na₂SO₄, concentrating under vacuo and distillation gave **13** (159.6 g, 67%) as an oil that crystallized on standing. – B.p. 110–125 °C/0.07 mm. – ¹H NMR (CDCl₃, 300 MHz): δ = 1.2–1.4 {m, 4 H, (CH₂)₂}, 1.5–1.7 (quint, *J* = 7.5 Hz, 2 H, CH₂–CH₂–COO), 1.6–1.8 (quint, *J* = 7.5 Hz, 2 H, CH₂–CO), 2.3 (t, *J* = 7.5 Hz, 2 H, CH₂–COO), 2.8 (t, *J* = 7.5 Hz, 2 H, CH₂–CO), 3.6 (s, 3 H, CH₃O), 6.5 (dd, *J* = 3.4, 1.8 Hz, 1 H, ArCH–ArCH–O), 7.2 (dd, *J* = 3.4, 0.9 Hz, 1 H, ArCH–ArC), 7.6 (dd, *J* = 1.8, 0.9 Hz, 1 H, ArCH–O). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 23.9 (CH₂–CH₂–CO), 24.6 (CH₂–CH₂–COO), 28.7 {2 C, (CH₂)₂–(CH₂)₂–CO}, 33.8 (CH₂–COO), 38.2 (CH₂–CO), 51.3 (CH₃O), 112.1 (ArCH–ArCH–O), 116.7 (ArCH–ArC), 146.2 (ArC–O), 152.9 (ArC–CO), 174.2 (COO), 189.7 (CO).

Methyl-8-furyl-8-hydroxy-octanoate (14): To a solution of **13** (100.0 g, 0.42 mol) in MeOH (500 mL) at 0°C was added NaBH₄ (15.9 g, 0.42 mol), in small portions, until the starting material was consumed. After removal of the MeOH under reduced pressure the crude product was dissolved in EtOAc (300 mL) and washed with saturated aqueous NaHSO₄ (200 mL) and brine (200 mL). Drying over Na₂SO₄ and elimination of the solvent under vacuum afforded **14** (95.9 g, 95%). – ¹H NMR (CDCl₃, 300 MHz): δ = 1.3 {m, 6 H, (CH₂)₃}, 1.6 (quint, *J* = 7.5 Hz, 2 H, CH₂–CH₂–COO), 1.8 (m, 2 H, CH₂–CH–OH), 2.3 (t, *J* = 7.5 Hz, 2 H, CH₂–COO), 3.6 (s, 3 H, CH₃O), 4.6 (t, *J* = 6.9 Hz, 1 H, CH–OH), 6.2 (dt, *J* = 3.3, 0.7 Hz, 1 H, ArCH–ArC), 6.3 (dd, *J* = 3.3, 1.8 Hz, 1 H, ArCH–ArCH–O), 7.4 (dd, *J* = 1.8, 0.7 Hz, 1 H, ArCH–O). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 24.7 (CH₂), 25.2 (CH₂), 28.9 (2 × CH₂), 33.9 (CH₂–COO), 35.4 (CH₂–CH–OH), 51.3 (CH₃O), 67.8 (CH–OH), 105.7 (ArCH–ArC), 110.1 (ArCH–ArCH–O), 141.9 (ArCH–O), 157.0 (ArC), 174.3 (COO).

Methyl-7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptanoate (16): Compound **14** (90 g, 0.37 mol) was dissolved in dioxane (500 mL), stabilized with hydroquinone (50 mg), and added to a solution of ZnCl₂ (190.8 g, 1.4 mol) in water (330 mL). The reaction mixture was refluxed for 6 hours. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (300 mL) and washed twice with a saturated solution of NaHCO₃ (100 mL) in order to remove the small amount of free acid generated during the reaction. The EtOAc phase was washed with brine (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure affording a mixture of **15** and **16**. The crude mixture of **15** and **16** was dissolved in toluene (500 mL) and treated with Et₃N (33.9 mL, 0.24 mol) and anhydrous chloral (3.3 g, 22.5 mmol). The solution was stirred until TLC showed completion of the reaction. Filtration through a column of silica gel and removal of the solvent under reduced pressure afforded **16** (64.8 g, 72%) as a yellow oil which solidified at 4°C. Crude **16** was used without further purification for the enzymatic resolution.

Methyl-7-[3(*R*)-hydroxy-5-oxo-1-cyclopenten-1-yl]-heptanoate (6): A mixture of **16** (30.0 g, 0.12 mol) and porcine pancreatic lipase (PPL, Sigma, EC 3.1.1.3) (30 g) in vinyl acetate (250 mL) was vigorously stirred at room temperature for 7 days. The suspension was filtered through celite and the solvent evaporated under reduced pressure affording 34.0 g of a crude mixture of **17** and **18** which was used for the following procedures without further purification.

Method A: A crude mixture of **17** and **18** (34.0 g), obtained from the enzymatic reaction, was dissolved in THF (250 mL) and triphenylphosphane (31.5 g, 0.12 mol) and formic acid (4.5 mL, 0.12 mol) were added. The solution was cooled to –5°C and treated with diethyl azodicarboxylate (39.3 mL, 0.25 mol) keeping the temperature below 15°C. The reaction mixture was warmed to room temperature and stirred overnight. The solvent was evaporated and the oily residue dissolved in Et₂O (300 mL) followed by the addition of pentane (200 mL). After stirring for 30 minutes the mixture was filtered and evaporated affording a mixture of acetate and formate derivatives. The crude was dissolved in MeOH (300 mL) and cooled to 0°C followed by the addition of a 0.5 M solution of guanidine in MeOH (132.0 mL, 66.0 mmol). The mixture was stirred for 15 minutes and neutralized with glacial acetic acid (3.8 mL, 66.0 mmol). The solvent was removed under reduced pressure and the residue was partitioned between water (250 mL) and EtOAc (250 mL). The aqueous layer was further extracted with EtOAc (250 mL) and the combined organic phases were washed with water (100 mL) and brine (100 mL), and dried over Na₂SO₄. The crude product was purified by flash chromatography affording

6 (22.8 g, 76%). The *ee* value was determined to be 96% by chiral HPLC analysis: Chiracel OB (250 × 4.6 mm), mobile phase: hexane/*i*PrOH 90:10, flow rate: 1.0 mL/min, λ = 210 nm, *R*_T (*R*-isomer) = 30.8 min, *R*_T (*S*-isomer) = 37.7 min. Chiracel OD (250 × 4.6 mm), mobile phase: hexane/*i*PrOH 95:5, flow rate: 0.8 mL/min, λ = 210 nm, *R*_T (*S*-isomer) = 52.3 min, *R*_T (*R*-isomer) = 55.8 min.

Method B: A crude mixture of **17** and **18** (34.0 g), obtained from the enzymatic reaction, was dissolved in CH₂Cl₂ (300 mL) and cooled to –10°C. Et₃N (10.4 mL, 74.9 mmol) was added followed by dropwise addition of methanesulfonyl chloride (5.3 mL, 68.7 mmol). When the reaction reached completion, a saturated solution of NaHCO₃ (50 mL) was added followed by water (50 mL) and CH₂Cl₂ (100 mL). The organic phase was separated, dried over Na₂SO₄ and concentrated in vacuo affording a mixture of **17** and **18a**. A small sample was purified by flash chromatography for analysis. The residue was dissolved in dioxane/H₂O (1:1, 400 mL) and treated with NaOAc·3H₂O (40.8 g, 0.3 mol) at room temperature for 12 hours. The dioxane was evaporated under vacuum and the residue extracted with EtOAc (300 mL), washed with water (100 mL) and brine (100 mL), and dried over Na₂SO₄ affording a mixture of (*R*)-acetate **17** and (*R*)-hydroxy **6**. An analytical sample was hydrolyzed with guanidine, as described above, and the *ee* value was determined to be 84% using the analysis described in method A.

Method B': The crude mixture of **17** and **6**, obtained in method B, was dissolved in vinyl acetate (250 mL) and treated with PPL (Sigma, EC 3.1.1.3) (30 g) for 7 days. The enzyme was separated by filtration through celite and the solvent removed under vacuum. The crude was dissolved in toluene (175 mL) and added to a stirred suspension of LiBr (17.4 g, 0.2 mol) in hexane/toluene 1:1 (200 mL). After 2 h stirring, the LiBr complex of **18** was removed by filtration and the filtrate was concentrated to give **17**. The (*R*)-acetate **17** was dissolved in MeOH (300 mL) and cooled to 0°C followed by the addition of a 0.5 M solution of guanidine in MeOH (132.0 mL, 66.0 mmol). The mixture was stirred for 15 minutes and neutralized with glacial acetic acid (3.8 mL, 66.0 mmol). The solvent was removed under reduced pressure and the residue was partitioned between water (250 mL) and EtOAc (250 mL). The aqueous layer was further extracted with EtOAc and the combined organic layers were washed with water (100 mL) and brine (100 mL), and dried over Na₂SO₄ affording **6** (23.7 g, 79%). The *ee* value was determined to be 94% using the analysis described in method A.

Method C: A crude mixture of **17** and **18** (34.0 g), obtained from the enzymatic reaction, was converted into **17** and **18a** as described in method B. The crude mixture was dissolved in CH₃CN (300 mL) and treated at room temperature with CsOAc (35.9 g, 0.19 mol) until the mesylate was consumed. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (300 mL), washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated in vacuo affording the (*R*)-acetate **17**. **17** was hydrolyzed as described above (method B') affording **6** (25.5 g, 85%). The *ee* value was determined to be 91% using the analysis described in method A.

Method D: A crude mixture of **17** and **18** (1.7 g), obtained from the enzymatic reaction, was converted into **17** and **18a** as described in method B. The residue was dissolved in CH₃CN (25 mL) and treated at room temperature with CsOAc (1.7 g, 9.0 mmol) and 18-crown-6 (79 mg, 0.3 mmol) until the mesylate was consumed. The solvent was removed under reduced pressure and the residue dissolved in EtOAc (50 mL), washed with water (20 mL) and brine (20 mL), dried over Na₂SO₄ and concentrated in vacuo affording

the (*R*)-acetate **17**. **17** was hydrolyzed as described above (method B'). The crude product was purified by flash chromatography affording **6** (1.2 g, 80%). The *ee* value was determined to be 92% using the analysis described in method A.

Method E: A crude mixture of **17** and **18** (1.7 g), obtained from the enzymatic reaction, was converted into **17** and **18a** as described in method B. The residue was dissolved in DMF (25 mL) and CsF (2.3 g, 15.0 mmol) was added. The solution was cooled to 0°C and acetic acid glacial (0.86 mL, 15.0 mmol) was added. The mixture was brought to room temperature and stirred until the mesylate was consumed. The reaction was poured over EtOAc/ice-water (2:1) (100 mL) and the organic phase was separated, washed with saturated solution of NaHCO₃ (25 mL), water (4 × 25 mL) and brine (25 mL), and dried over Na₂SO₄ affording the (*R*)-acetate **17**. **17** was hydrolyzed as described above (method B'). The crude product was purified by flash chromatography affording **6** (1.1 g, 73%). The *ee* value was determined to be 91% using the analysis described in method A.

Method F: A crude mixture of **17** and **18** (1.7 g), obtained from the enzymatic reaction, was converted into **17** and **18a** as described in method B. The residue was dissolved in dioxane/H₂O 1:1 (20 mL) and treated with NaOAc·3H₂O (2.0 g, 15 mmol) and CsF (2.3 g, 15 mmol) at room temperature for 12 hours. The dioxane was evaporated under vacuum and the residue extracted with EtOAc (50 mL), washed with water (20 mL) and brine (20 mL), and dried over Na₂SO₄ affording a mixture of (*R*)-acetate **17** and (*R*)-hydroxy **6**. Hydrolysis as described above (method B') and flash chromatography afforded **6** (1.12 g, 75%). The *ee* value was determined to be 81% using the analysis described in method A.

Method G: A crude mixture of **17** and **18** (1.7 g), obtained from the enzymatic reaction, was converted into **17** and **18a** as described in method B. The residue was dissolved in MeOH (15 mL) and cooled to 0°C followed by the addition of a 0.2 M solution of guanidine in MeOH (16.5 mL, 3.3 mmol). The mixture was stirred until TLC checking showed completion and then neutralized with glacial acetic acid (0.19 mL, 3.3 mmol). The solvent was removed under reduced pressure and the residue was partitioned between water (25 mL) and EtOAc (25 mL). The aqueous layer was further extracted with EtOAc (25 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL), and dried over Na₂SO₄. The crude product was purified by flash chromatography affording **6** (1.23 g, 82%). The *ee* value was determined to be 80% using the analysis described in method A.

Mesylate derivative (18a): ¹H NMR (CDCl₃, 300 MHz): δ = 1.3 {m, 4 H, (CH₂)₂}, 1.5 (m, 2 H, CH₂–CH₂–C=), 1.6 (m, 2 H, CH₂–CH₂–COO), 2.2 (tt, *J* = 7.7, 1.4 Hz, 2 H, CH₂–C=), 2.3 (t, *J* = 7.5 Hz, 2 H, CH₂–COO), 2.5 (dd, *J* = 18.9, 1.8 Hz, 1 H, 1H CH₂–CO), 2.8 (dd, *J* = 18.9, 6.3 Hz, 1 H, 1H CH₂–CO), 3.0 (s, 3 H, CH₃–S), 3.6 (s, 3 H, CH₃O), 5.7 (m, 1 H, CH–OMs), 7.1 (dt, *J* = 2.6, 1.4 Hz, 1 H, CH=). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 24.3 (CH₂–C=), 24.5 (CH₂–CH₂–COO), 26.8 (CH₂–CH₂–C=), 28.5 and 28.6 {(CH₂)₂–(CH₂)₂–COO}, 33.7 (CH₂–COO), 38.4 (CH₃–S), 41.3 (CH₂–CO), 51.2 (CH₃O), 75.6 (CH–OMs), 149.9 (CH=), 151.4 (C=), 174.1 (COOCH₃), 202.9 (CO).

Acetate derivative (17): ¹H NMR (CDCl₃, 300 MHz): δ = 1.2–1.4 {m, 4 H, (CH₂)₂}, 1.4 (m, 2 H, CH₂–CH₂–C=), 1.5 (m, 2 H, CH₂–CH₂–COO), 2.0 (s, 3 H, CH₃–CO), 2.1 (br. t, *J* = 7.5 Hz, 2 H, CH₂–C=), 2.2 (t, *J* = 7.5 Hz, 2 H, CH₂–COO), 2.3 (dd, *J* = 18.9, 2.1 Hz, 1 H, 1H CH₂–CO), 2.8 (dd, *J* = 18.9, 6.3 Hz, 1 H, 1H CH₂–CO), 3.6 (s, 3 H, CH₃O), 5.7 (m, 1 H, CH–OAc), 7.1 (m, 1 H, CH=). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 20.7

(CH₃–COO), 24.3 (CH₂–C=), 24.5 (CH₂–CH₂–COO), 26.9 (CH₂–CH₂–C=), 28.5 and 28.7 {(CH₂)₂}, 33.8 (CH₂–COO), 41.3 (CH₂–CO), 51.2 (CH₃O), 70.3 (CH–OAc), 149.9 (C=), 151.6 (CH=), 170.6 (CH₃–COO), 174.1 (COOCH₃), 204.8 (CO).

Hydroxy derivative (6): ¹H NMR (CDCl₃, 300 MHz): δ = 1.2–1.4 {m, 4 H, (CH₂)₂}, 1.5 (quint, *J* = 7.6 Hz, 2 H, CH₂–CH₂–C=), 1.6 (quint, *J* = 7.3 Hz, 2 H, CH₂–CH₂–COO), 2.1 (br. t, *J* = 7.6 Hz, 2 H, CH₂–C=), 2.3 (t, *J* = 7.3 Hz, 2 H, CH₂–COO), 2.3 (dd, *J* = 18.5, 1.8 Hz, 1 H, 1H CH₂–CO), 2.6 (br. s, 1 H, OH), 2.8 (dd, *J* = 18.5, 6.1 Hz, 1 H, 1 H CH₂–CO), 3.6 (s, 3 H, CH₃O), 4.9 (m, 1 H, CH–OH), 7.2 (m, 1 H, CH=). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 24.2 (CH₂–C=), 24.7 (CH₂–CH₂–COO), 27.1 (CH₂–CH₂–C=), 28.6 and 28.7 {(CH₂)₂}, 33.9 (CH₂–COO), 44.9 (CH₂–CO), 51.3 (CH₃O), 68.5 (CH–OH), 148.0 (C=), 155.9 (CH=), 174.4 (COO), 206.3 (CO).

Methyl-7-[5-oxo-3(*R*)-[(triethylsilyl)oxy]-1-cyclopenten-1-yl]-heptanoate (20): To a solution of **6** (45 g, 0.18 mol) and Et₃N (78.2 mL, 0.56 mol) in THF (350 mL) at 0°C was added dropwise Et₃SiCl (47.1 mL, 0.28 mol). The solution was stirred at 20°C until TLC showed completion of the reaction and then filtered through celite and concentrated. The residue was dissolved in hexane (200 mL), filtered again through celite and the solvent was evaporated under reduced pressure affording crude **20** that was purified by bulb-to-bulb distillation (150–160°C/0.1 mm). **20** was obtained as a light yellow oil (58.4 g, 88%). Deprotection of a small sample and analysis by chiral HPLC showed that no epimerization had occurred during silylation and distillation. – ¹H NMR (CDCl₃, 300 MHz): δ = 0.6 (q, *J* = 8.0 Hz, 6 H, CH₂–Si), 0.9 (t, *J* = 8.0 Hz, 9 H, CH₃–CH₂–Si), 1.2–1.4 {m, 4 H, (CH₂)₂}, 1.4–1.5 (m, 2 H, CH₂–CH₂–C=), 1.5–1.7 (m, 2 H, CH₂–CH₂–COO), 2.1–2.2 (m, 2 H, CH₂–C=), 2.3 (dd, *J* = 18.3, 2.1 Hz, 1 H, 1H CH₂–CO), 2.3 (t, *J* = 7.5 Hz, 2 H, CH₂–COO), 2.7 (dd, *J* = 18.3, 5.7 Hz, 1 H, 1H CH₂–CO), 3.7 (s, 3 H, CH₃O), 4.9 (m, 1 H, CH–OTES), 7.0 (m, 1 H, CH=). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 4.7 (3 C, CH₂–Si), 6.6 (3 C, CH₃–CH₂–Si), 24.3 (CH₂–C=), 24.7 (CH₂–CH₂–COO), 27.1 (CH₂–CH₂–C=), 28.7 and 28.9 {(CH₂)₂}, 33.9 (CH₂–COO), 45.5 (CH₂–CO), 51.3 (CH₃O), 68.6 (CH–OTES), 147.2 (C=), 156.5 (CH=), 174.1 (COO), 206.1 (CO).

(*S*)-1-Iodo-1(*E*)-octen-3-ol (7): In a flame dried flask under argon containing a solution of an *n*-butylboronic complex of diphenyl D-prolinol (1.6 g, 5.0 mmol) in toluene (250 mL) was added 1-iodo-1(*E*)-octen-3-one (**19**) (25.0 g, 0.10 mol) and the solution was cooled to –78°C. To this mixture was added a 4 M solution of catecholborane in toluene (50.0 mL, 0.20 mol) over 12 hours. After 24 hours at –78°C the reaction was quenched by dropwise addition of MeOH (10 mL) and the reaction was allowed to reach 0°C over 1 hour. The solution was extracted six times with 4 N NaOH (50 mL), extracted twice with 10% HCl (50 mL), washed once with brine (200 mL), dried over Na₂SO₄ and evaporated under reduced pressure to afford **7** (24.1 g, 95%). The *ee* value was determined to be >96% by ¹H NMR of the Mosher ester derivative and by chiral HPLC analysis: Chiracel OF (250 × 4.6 mm), mobile phase: hexane/*i*PrOH 97.5:2.5, flow rate: 0.5 mL/min, λ = 210 nm, *R*_T (*R*-isomer) = 14.7 min, *R*_T (*S*-isomer) = 16.6 min. – ¹H NMR (CDCl₃, 300 MHz): δ = 0.9 (t, *J* = 6.9 Hz, 3 H, CH₃), 1.2–1.4 {m, 6 H, (CH₂)₃–CH₃}, 1.4–1.6 (m, 2 H, CH₂–CH–OH), 4.1 (dq, *J* = 6.3, 1.1 Hz, 1 H, CH–OH), 6.3 (dd, *J* = 14.4, 1.1 Hz, 1 H, =CH–I), 6.6 (dd, *J* = 14.4, 6.3 Hz, 1 H, =CH–CH–OH). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 13.9 (CH₃), 22.4 (CH₂–CH₃), 24.7 (CH₂–CH₂–CO), 31.5 (CH₂–CH₂–CH₃), 36.5 (CH₂–CH–OH), 74.6 (CH–OH), 77.0 (=CH–I), 148.8 (=CH–CH–OH).

(S)-1-Iodo-3-[(trimethylsilyloxy)-1-(E)-octene (21): Compound **7** (24.0 g, 94.4 mmol), Et₃N (19.7 mL, 0.14 mol) and imidazole (18.0 g, 0.26 mol) were dissolved in DMF (100 mL). The solution was cooled at 0–5°C and Me₃SiCl (13.2 mL, 0.10 mol) was added dropwise. The solution was stirred at 20°C until TLC showed completion of the reaction. The reaction mixture was diluted with hexane (250 mL) and washed twice with ice-water (200 mL) and brine (200 mL). Drying over Na₂SO₄ and removing the solvent under vacuum provided **21** (29.9 g, 97%). – ¹H NMR (CDCl₃, 300 MHz): δ = 0.1 (s, 9 H, CH₃–Si), 0.9 (t, *J* = 6.8 Hz, 3 H, CH₃), 1.2–1.4 {m, 6 H, (CH₂)₃–CH₃}, 1.4–1.6 (m, 2 H, CH₂–CH–O), 4.0 (dq, *J* = 6.0, 0.9 Hz, 1 H, CH–O), 6.2 (dd, *J* = 14.4, 0.9 Hz, 1 H, =CH–I), 6.5 (dd, *J* = 14.4, 6.0 Hz, 1 H, =CH–CH–O). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 0.1 (3C, CH₃–Si), 13.9 (CH₃), 22.5 (CH₂–CH₃), 24.8 (CH₂–CH₂–CH₃), 31.6 {CH₂–(CH₂)₂–CH₃}, 37.3 (CH₂–CH–O), 75.1 (CH–O), 75.6 (=CH–I), 149.2 (=CH–CH–O).

PGE₁ methyl ester (22): To a solution of **21** (20 g, 61.2 mmol) in Et₂O (70 mL) at –78°C, in a flame-dried flask under argon, was added dropwise a 1.6 M solution of *n*BuLi in hexane (40 mL, 64.3 mmol). The resulting solution was stirred at –78°C for 2 hours. CuCN (5.5 g, 61.2 mmol) was placed in a second flame-dried flask and suspended in Et₂O (180 mL). The mixture was cooled at –78°C and a 1.5 M solution of MeLi in Et₂O (41.6 mL, 62.3 mmol) was slowly added. After 45 minutes at 0°C the clear solution was cooled again to –78°C and the previously prepared vinylolithium reagent was added with a cannula. The reaction was slowly warmed to –30°C and kept for 20 minutes at this temperature before recooling to –78°C for the addition of **20** (10.9 g, 30.7 mmol) in Et₂O (70 mL). After 20 minutes the reaction mixture was poured into a solution of 9:1 saturated aqueous NH₄Cl/NH₄OH (150 mL), layered with Et₂O (150 mL). The mixture was vigorously stirred for 30 minutes. The organic layer was separated and washed three times with a mixture of 9:1 saturated aqueous NH₄Cl/NH₄OH solution (100 mL) and once with brine (100 mL). The organic phase was dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was dissolved in acetone (150 mL) and water (30 mL) and treated with pyridinium *p*-toluenesulfonate (150 mg). After 4 hours stirring at room temperature the solvent was removed under vacuum and the residue partitioned between EtOAc (150 mL) and brine (100 mL). The layers were separated and the aqueous phase extracted twice with EtOAc (100 mL). The combined organic phases were washed with brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Removal of less polar by-products was achieved by extracting a solution of crude **22** in CH₃CN (300 mL) with hexane (3 × 100 mL). The CH₃CN was evaporated under vacuum affording PGE₁ methyl ester (**22**) (9.6 g, 85%). – ¹H NMR (CDCl₃, 300 MHz): δ = 0.8 (t, *J* = 6.6 Hz, 3 H, CH₃), 1.2–1.4 (m, 12 H, 6 × CH₂), 1.4–1.7 (m, 6 H, CH₂–CH₂–COO, CH₂–CH–CO, CH₂–CH–OH), 1.9 (m, 1 H, CH–CO), 2.1 (dd, *J* = 18.5, 9.9 Hz, 1 H, 1H CH₂–CO), 2.3 (t, *J* = 7.5 Hz, 2 H, CH₂–COO), 2.3 (m, 1 H, CH–CH=), 2.7 (dd, *J* = 18.5, 7.1 Hz, 1 H, 1H CH₂–CO), 3.0 (br. s, 1 H, OH), 3.6 (s, 3 H, CH₃O), 4.0 (br. s, 1 H, OH), 4.0 (m, 1 H, HO–CH–CH₂–CO), 4.1 (m, 1 H, HO–CH–CH=), 5.5 (dd, *J* = 15.3, 8.7 Hz, 1 H, CH=CH–CH–OH), 5.6 (dd, *J* = 15.3, 1 H, 7.5 Hz, =CH–CH–OH). – ¹³C NMR (CDCl₃, 75.5 MHz): δ = 13.9 (CH₃), 22.5 (CH₂–CH₃), 24.7 (CH₂–CH₂–COO), 25.0 (CH₂–(CH₂)₂–CH₃), 26.5 (CH₂–(CH₂)₄–COO), 27.6 (CH₂–(CH₂)₅–COO), 28.8 and 29.2 {(CH₂)₂–(CH₂)₂–COO}, 31.6 (CH₂–CH₂–CH₃), 33.9 (CH₂–COO), 37.2 (CH₂–CH–OH), 45.8 (CH₂–CO), 51.4 (CH₃O), 54.4 (CH–CO), 54.8 (CH–CH=), 71.8 (HO–CH–CH₂–CO), 73.0 (HO–CH–CH=), 132.1 (CH=

CH–CH–OH), 136.8 (=CH–CH–OH), 174.3 (COO), 214.7 (CO).

(–)-PGE₁(5): A suspension of porcine pancreatic lipase (PPL, Sigma, EC 3.1.13, 1 g), NaCl (50 mg) and CaCl₂ (150 mg) in water (150 mL) was adjusted to pH 7.1 before **22** (9 g, 24.4 mmol) in THF (25 mL) was added. The pH was maintained between 7.0–7.2 by the addition of 0.1 N NaOH solution. After 30 minutes without pH changes, the solvent was removed under vacuum, the residue was layered with EtOAc (50 mL), and solid KHSO₄ (8.0 g, 58.8 mmol) and NaCl (30 g) were added. The aqueous phase was extracted with additional portions of EtOAc (6 × 50 mL). Drying over Na₂SO₄ and concentrating in vacuo afforded crude **5** that was recrystallized from hot EtOAc to give (–)-PGE₁ (**5**) (7.7 g, 89%) as colorless needles, m.p. 113–115°C (ref.^[54] 115–116°C), [α]_D²⁰ = –56.3 (*c* = 0.49, THF) {ref.^[54] [α]_D²¹ = –55.0 (*c* = 0.73, THF)}. – ¹H NMR (CDCl₃/D₆acetone, 300 MHz): δ = 0.8 (t, *J* = 6.6 Hz, 3 H, CH₃), 1.1–1.3 (m, 12 H, 6 × CH₂), 1.3–1.6 (m, 6 H, CH₂–CH₂–COO, CH₂–CH–CO, CH₂–CH–OH), 1.9 (m, 1 H, CH–CO), 2.1 (dd, *J* = 18.6, 9.9 Hz, 1 H, 1H CH₂–CO), 2.2 (t, *J* = 7.3 Hz, 2 H, CH₂–COO), 2.3 (dt, *J* = 12.0, 8.4 Hz, 1 H, CH–CH=), 2.7 (ddd, *J* = 18.5, 7.5, 1.3 Hz, 1 H, 1H CH₂–CO), 3.9–4.1 (m, 2 H, 2 × CH–OH), 5.5 (dd, *J* = 15.3, 8.4 Hz, 1 H, CH=CH–CH–OH), 5.6 (dd, *J* = 15.3, 7.2 Hz, 1 H, =CH–CH–OH). – ¹³C NMR (CDCl₃/D₆acetone, 75.5 MHz): δ = 13.7 (CH₃), 22.4 (CH₂–CH₃), 24.5 (CH₂–CH₂–COO), 24.9 (CH₂–(CH₂)₂–CH₃), 26.3 (CH₂–(CH₂)₄–COO), 27.4 (CH₂–(CH₂)₅–COO), 28.6 and 29.0 ((CH₂)₂–(CH₂)₂–COO), 31.5 (CH₂–CH₂–CH₃), 33.8 (CH₂–COO), 36.7 (CH₂–CH–OH), 45.7 (CH₂–CO), 54.2 (CH–CO), 54.5 (CH–CH=), 71.5 (HO–CH–CH₂–CO), 72.9 (HO–CH–CH=), 132.0 (CH=CH–CH–OH), 136.6 (=CH–CH–OH), 177.0 (COO), 215.5 (CO). – IR: 3343, 2923, 2853, 1725, 1702, 1411, 1359, 1318, 1275, 1245, 1219, 1171, 1125, 1111, 1078, 1019, 979, 967 cm^{–1}. – AP-1–ES/MS (*m/z*): 353 [M_{PGE1}–H⁺][–], 317 [M_{PGE1}–(2H₂O)–H⁺][–], 707 [2M_{PGE1}–H⁺][–], 729 [2M_{PGE1}+Na⁺–2H⁺][–].

Acknowledgments

Financial support of this research in part by Laboratorios Lasa S.A., Barcelona (Spain), and the Department of Cell Biology UMDNJ-SOM is gratefully acknowledged. We thank Prof. Dr. M. Hamberg of the Karolinska Institute, Stockholm (Sweden), for the determination of the C-15 (S)-purity in **5**.

- [1] [1a] P. Needleman, P. C. Isakson, *J. Rheumatol.* **1997**, *24*, 6–8. – [1b] J. L. Masferrer, K. Seibert, B. Zweifel, P. Needleman, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 3917–3921.
- [2] S. Berstrom, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 858–866.
- [3] P. Sestini, L. Armetti, G. Gambaro, M. G. Pieroni, R. M. Refini, A. Sala, A. Vaghi, G. C. Folco, S. Bianco, M. Robuschi, *Am. J. Respir. Crit. Care Med.* **1996**, *153*, 572–575.
- [4] I. M. Spitz, C. W. Bardin, L. Benton, A. Robbins, *N. Engl. J. Med.* **1998**, *338*, 1241.
- [5] G. Williams, C. C. Abbou, E. T. Amar, P. Desvaux, T. A. Flam, G. A. Lycklama, S. F. Lynch, R. J. Morgan, S. C. Muller, H. Porst, J. P. Prior, P. Ryan, U. K. Witzsch, M. M. Hall, V. A. Place, A. P. Spivack, N. Gesundheit, *Br. J. Urol.* **1998**, *81*, 889–894.
- [6] C. Liljebriis, B. Resul, U. Hacksell, *Bioorg. Med. Chem. Lett.* **1993**, *3*, 241–244.
- [7] J. D. Morrow, J. A. Awad, H. J. Boss, I. A. Blair, L. J. Roberts II, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 10721–10725.
- [8] D. Pratico, V. M.-Y. Leeh, J. Q. Trojanowski, J. Rokach, G. A. Fitzgerald, *FASEB J.* **1998**, *12* (15), 1777–1783.
- [9] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc.* **1969**, *91*, 5675–5676.

- [10] P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, 93, 1533–1564.
- [11] E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, 97, 6908–6909.
- [12] E. J. Corey, N. Imai, S. Pikul, *Tetrahedron Lett.* **1991**, 32, 7517–7520.
- [13] I. Fleming, S. B. D. Winter, *J. Chem. Soc., Perkin Trans. 1* **1998**, 17, 2687–2700.
- [14] E. J. Corey, K. B. Becker, R. K. Varma, *J. Am. Chem. Soc.* **1972**, 94, 8616–8618.
- [15] E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, 109, 7925–7926.
- [16] S. Iguchi, H. Nakai, M. Hayashi, H. Yamamoto, K. Maruoka, *Bull. Chem. Soc. Jpn.* **1981**, 54, 3033–3041.
- [17] R. Noyori, I. Tomino, M. Yamada, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, 106, 6717–6725.
- [18] W. Bartmann, G. Beck, G. Jahne, U. Lerch, G. Wess, *Liebigs Ann. Chem.* **1987**, 321–327.
- [19] K. B. Mallion, G. E. Robinson, *United States Patent* 4,079,055 (Imperial Chemical Industries Ltd.) **1978**.
- [20] [20a] G. Kobzar, V. Mardla, I. Jarving, M. Lohmus, A. Vahemets, N. Samel, U. Lille, *Comp. Biochem. Physiol. C* **1993**, 106, 489–494. — [20b] E. J. Corey, R. Noyori, T. K. Schaaf, *J. Am. Chem. Soc.* **1970**, 92, 2586–2587.
- [21] [21a] F. S. Alvarez, D. Wren, A. Prince, *J. Am. Chem. Soc.* **1972**, 94, 7823–7827. — [21b] A. F. Kluge, K. G. Untch, J. H. Fried, *J. Am. Chem. Soc.* **1972**, 94, 7827–7832.
- [22] [22a] P. W. Collins, *Chronicles of Drug Discovery* (Ed.: D. Lednicer), American Chemical Society, Washington, DC, **1993**, 3, 101–124. — [22b] P. W. Collins, E. Z. Dajani, D. R. Driskill, M. S. Bruhn, C. J. Jung, R.-J. Pappo, *J. Med. Chem.* **1977**, 20, 1152–1159. — [22c] B. A. Lipshutz, E. L. Ellsworth, *J. Am. Chem. Soc.* **1990**, 112, 7440–7441.
- [23] R. Pappo, P. Collins, C. Jung, *Tetrahedron Lett.* **1973**, 12, 943–944.
- [24] [24a] K. A. Babiak, J. S. Ng, J. H. Dygos, C. L. Weyker, *J. Org. Chem.* **1990**, 55, 3377–3381. — [24b] C.-H. Wong, Y.-F. Wang, W. J. Hennen, K. A. Babiak, J. H. Dygos, J. S. Ng, *United States Patent* 5,106,750 (G. D. Searle and Co.) **1992**.
- [25] M. Suzuki, A. Yanagisawa, R. Noyori, *J. Am. Chem. Soc.* **1988**, 110, 4718–4726.
- [26] J. L. Leighton, E. Jacobsen, *J. Org. Chem.* **1996**, 61, 389–390.
- [27] O. W. Gooding, C. C. Beard, G. B. Cooper, D. Y. Jackson, *J. Org. Chem.* **1993**, 58, 3681–3686.
- [28] C. R. Johnson, M. P. Braun, *J. Am. Chem. Soc.* **1993**, 115, 11014–11015.
- [29] A. Rodríguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Tetrahedron Lett.* **1998**, 39, 8563–8566.
- [30] M. Lobell, M. P. Schneider, *J. Chem. Soc., Perkin Trans. 1* **1993**, 1713–1714.
- [31] M. Kondo, M. Minai, S. Kai, T. Higashi, Y. Ueda, *European Patent* A2,0,268,820 (Sumitomo Chemical Co. Ltd.) **1988**.
- [32] M. Minai, Y. Ueda, T. Higashii, M. Kondo, S. Kai, *European Patent* A2,0,247,620 (Sumitomo Chemical Co. Ltd.) **1987**.
- [33] G. Piancatelli, M. D'Auria, F. D'Onofrio, *Synthesis* **1994**, 867–889.
- [34] G. Stork, T. Takahashi, *J. Am. Chem. Soc.* **1977**, 99, 1275–1276.
- [35] O. Mitsunobu, M. Eguchi, *Bull. Chem. Soc. Jpn.* **1971**, 44, 3427–3430.
- [36] [36a] E. Vääntinen, L. Kanerva, *Tetrahedron: Asymmetry* **1995**, 6, 1779–1786. — [36b] S. Takano, M. Suzuki, K. Ogasawara, *Tetrahedron: Asymmetry* **1993**, 4, 1043–1046. — [36c] M.-J. Kim, I. S. Lee, *Synlett* **1993**, 767–768. — [36d] H. Danda, Y. Furukawa, T. Umemura, *Synlett* **1991**, 441–442. — [36e] U. T. Strauss, U. Felfer, K. Faber, *Tetrahedron: Asymmetry* **1999**, 10, 107–117. — [36f] K. Lemke, S. Ballschuh, A. Kunath, F. Theil, *Tetrahedron: Asymmetry* **1997**, 8, 2051–2055.
- [37] [37a] Y. Torisawa, H. Okabe, S. Ikegami, *Chem. Lett.* **1984**, 1555–1556. — [37b] T. Sato, J. Otera, *Synlett* **1995**, 336–338.
- [38] J. B. Hill, R. A. Erickson, *United States Patent* 4,452,994 (Searle and Co.) **1994**.
- [39] C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, S. S. Lee, *J. Am. Chem. Soc.* **1975**, 97, 865–874.
- [40] M. Shimizu, H. Kawanami, T. Fujisawa, *Chem. Lett.* **1992**, 107–110.
- [41] Y. Kitano, T. Matsumono, S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, *Chem. Lett.* **1987**, 1523–1526.
- [42] R. Noyori, I. Tomino, M. Nishizawa, *J. Am. Chem. Soc.* **1979**, 101, 5843–5844.
- [43] E. J. Corey, R. K. Bakshi, *Tetrahedron Lett.* **1990**, 31, 611–614.
- [44] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, 94, 6190–6191.
- [45] [45a] B. H. Lipshutz, M. R. Wood, *J. Am. Chem. Soc.* **1993**, 115, 12625–12626. — [45b] J. H. Dygos, J. P. Adamek, K. A. Babiak, J. R. Behling, J. R. Medich, J. S. Ng, J. J. Wiczarek, *J. Org. Chem.* **1991**, 56, 2549–2552.
- [46] C. N. Serhan, M. Hamberg, B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.* **1984**, 81, 5335–5339.
- [47] E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, R. E. K. Winter, *J. Am. Chem. Soc.* **1968**, 90, 3245.
- [48] S. Bergstrom, *Science* **1967**, 157, 382–391.
- [49] E. J. Corey, C. R. Cyr, *Tetrahedron Lett.* **1974**, 19, 1761–1763.
- [50] T. W. Hart, D. A. Metcalfe, F. Scheinmann, *J. Chem. Soc., Chem. Commun.* **1979**, 156–157.
- [51] E. J. Corey, R. K. Varma, *J. Am. Chem. Soc.* **1971**, 93, 7319–7320.
- [52] W. P. Schneider, *United States Patent* 3,959,346 (The Upjohn Company) **1976**.
- [53] J. Rokach, S. P. Khanapure, S.-W. Hwang, M. Adiyaman, L. Schio, G. A. FitzGerald, *Synthesis* **1998**, 569–580.
- [54] T. Tanaka, A. Hazato, K. Bannai, N. Okamura, S. Sugiura, K. Manabe, T. Toru, S. Kurozumi, M. Suzuki, T. Kawagishi, R. Noyori, *Tetrahedron* **1987**, 43, 813–824.

Received March 30, 1999
[O99187]