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Modular Enantioselective Synthesis of 8-Aza-prostaglandin E_1

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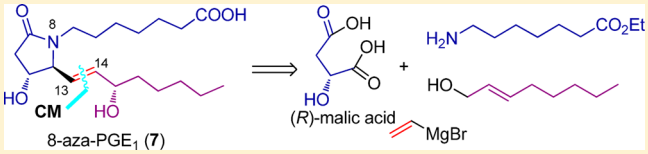
Supporting Information

ABSTRACT: We report herein for the first time the enantioselective synthesis of 8-aza-PGE_1. The synthesis used the cross olefin metathesis reaction to connect the 5-vinyl-γ-lactam subunit, prepared from (*R*)-malic acid via the Ley's sulfone-based α-amidalkylation protocol (dr = 6.8:1), with the chiral pre-ω-chain. The latter was synthesized in high enantioselectivity from (*E*)-2-octenol by the Sharpless asymmetric epoxidation and the titanocene-mediated epoxide opening. This modular approach is quite concise and flexible, and requires only eight steps from commercially available reagents.



Prostaglandins (PGs) are a group of naturally occurring lipid compounds found in trace amount in animals and in men. They are mediators and have a variety of strong physiological effects, which has made them very promising for the development of new therapeutic agents for a number of diseases.[1] Since the elucidation of their structures in the early 1960s, and throughout 1970s, the total synthesis of prostaglandins[2] has attracted tremendous attention of numerous chemists and pharmaceutical companies. These and the following studies have led to the development of many imaginative synthetic approaches and new chemistries, such as the three-component strategy.[3] However, due to the problems of the inherent instability, quick metabolism and side effects, the development of PGs as medicinal agents has been impeded.[2] To tackle these problems, much effort has been devoted to the synthesis of prostaglandin analogues. Up until 1984, over 5000 prostaglandin analogues have been synthesized and tested biologically.[3a] Those efforts resulted in the discovery of several drugs currently in clinical use,[1] which include prostaglandin E_1 (PGE_1, alprostadil) and the analogues of prostaglandins, such as Misoprostol (15-methyl-PGE_1, Cytotec; Anthrotec); Limaprost, Latanoprost (Xalatan), Carboprost (Hemabate), Bimatoprost (Lumigan), Travoprost (Travatan, Travatan Z, Travo-Z), Tafluprost (Ziopta, Taflotan), and so forth. Four of these pharmaceuticals entered the list of top 200 brand-name drugs by total US prescriptions in 2010.[4] In this context, many aza-analogues of PGE, in which a CH or a CH_2 of the cyclopentane ring is replaced by a nitrogen atom, have been synthesized.[5] The diastereomeric mixture of the 15α and 15β analogues was found to effectively interrupt pregnancy in the hamster and displayed only minimal smooth muscle activity relative to $PGF_{2\alpha}$.[5d]

In recent years, with the development of synthetic chemistry and progress in the identification and cloning of PG receptor subtypes,[6] there is renewed interest in the synthesis[7,8] and medicinal chemistry[8−11] of PGs, prostacyclins, isoprostanes, neuroprostanes, and their analogues. Highly efficient synthetic strategies have been developed[7] and several medicinal interesting γ-lactam analogues discovered.[9−11] For example, compound **2** was shown to be a potent and selective agonist of the prostaglandin EP_4;[9] CP-734432 (**3**) is a highly selective EP_4 receptor agonist with an IC_{50} = 2 nM;[10] PF-4475270 (**4**), the isopropyl ester prodrug of **3**, is a novel ocular hypotensive compound capable of effectively lowering intraocular pressure in dogs.

In spite of significant progress made in the chemistry and medicinal chemistry of 8-aza-analogues of PGs,[9−11] only 8-aza-11-deoxy analogues of PGs have so far been reported; the 8-aza-analogues of PGE_1 with the 11-hydroxyl group retained has never been reported. In light of the structure of PGE_1 (alprostadil), its medical usage,[12] and side effects,[13] it is worthwhile to develop a method for the enantioselective synthesis of 8-aza-PGE_1. Our group has long been interested in the asymmetric synthesis of bioactive *N*-containing compounds,[14] and recently reported the synthesis of two aza-prostaglandin analogues, namely, the 11-hydroxylated analogues of the lead compounds CP-734432 (**3**) and PF-04475270 (**4**), by SmI_2-mediated intermolecular coupling of lactam *N*-α-radicals with activated alkenes.[15] As a continuation of this study, we now report the synthesis of 8-aza-PGE_1 by a new strategy.

Among the strategies developed for the asymmetric synthesis of PGs, prostacyclins, and analogues,[2,3,5,7,8] the cross olefin metathesis-based strategy[7c−e,8c] is quite flexible for the installation of the chiral ω-chain. Inspired by this strategy, our retrosynthetic analysis of 8-aza-PGE_1 **7** is depicted in Scheme 1. A retro-cross olefin metathesis[16] disconnection of the protected 8-aza-PGE_1 **8** suggested 5-vinyl-pyrrolidin-2-one **9** and (*S*)-allylic alcohol **10** (pre-ω-chain) as the precursors. To further enhance both the efficiency and flexibility of the cross olefin metathesis-based strategy,[7d,e,8c] and in view of the problems in the creation of the stereogenic center at C15,[7d,e,8c] introduction of an efficient and flexible method for the

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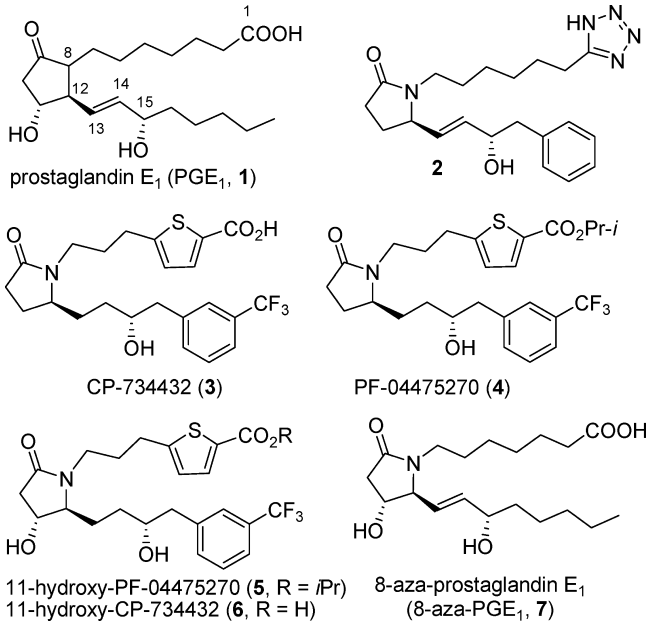
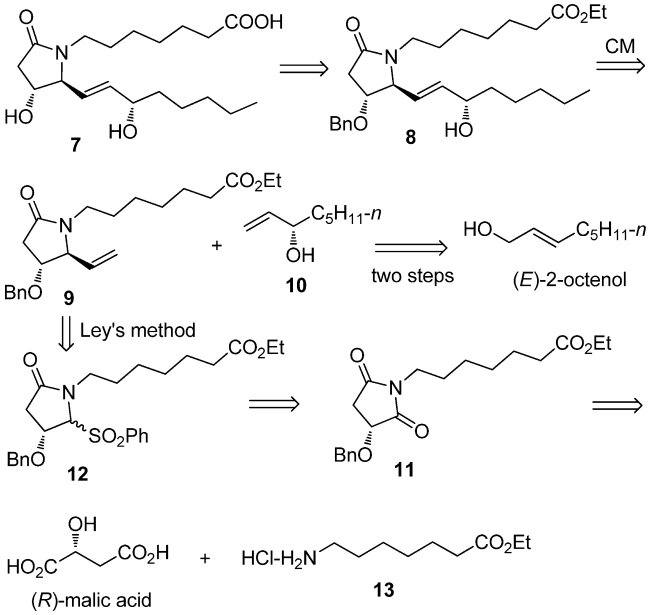


Figure 1. Prostaglandin E_1 and its 8-aza analogues.

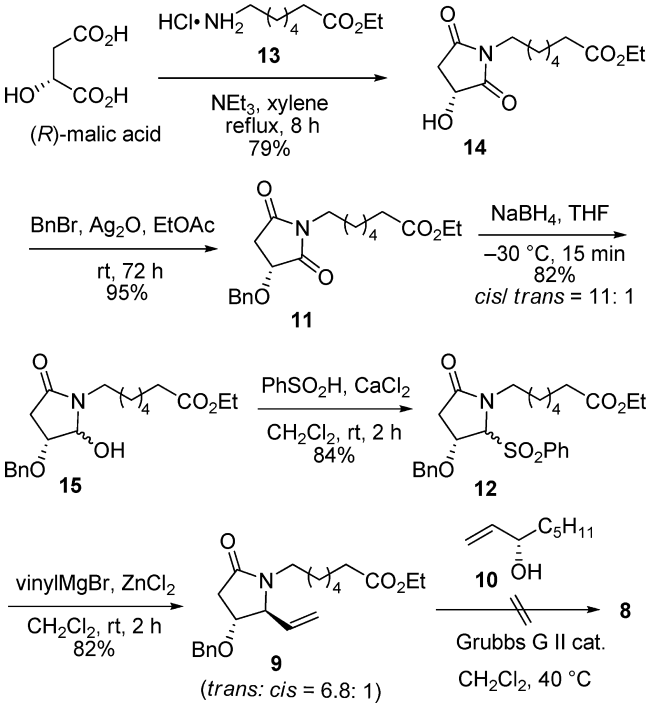
Scheme 1. Retrosynthetic Analysis of 8-aza-PGE$_1$ (7)



construction of the pre-ω-chain **10** in high enantioselectivity is highly desirable. In light of our recent work on the total synthesis of (+)-awajanomycin,[14d] the pre-ω-chain **10** was envisioned to be synthesized from commercially available (*E*)-2-octenol by a combination of Sharpless epoxidation[17] with the titanocene-mediated stereospecific epoxide opening, a method developed by Yadav and co-workers.[18] 5-Vinyl-pyrrolidin-2-one **9** could be accessible from malimide derivative **11** via α-amidovinylation of α-phenylsulfonyllactam **12** with the method developed by Ley and co-workers.[19] Finally, malimide **11** can be prepared by the condensation of commercially available (*R*)-malic acid and ethyl 7-aminoheptanoate hydrochloride salt **13**.

The synthesis started from the direct condensation of (*R*)-malic acid with the commercially available α,ω-amino ester hydrochloride salt **13** (Scheme 2). Although this condensation

Scheme 2



method is known for a long time,[20] its advantage in yielding racemization-free product was proven only very recently.[21] The desired malimide derivative **14** was thus produced in 79% yield by heating the mixture of (*R*)-malic acid and **13** in the presence of triethylamine in xylene at reflux for 8 h. The hydroxyl group of **14** was then protected to give benzyl ether **11** (BnBr, Ag_2O, EtOAc, rt, 72 h, yield: 95%). Treatment of malimide **11** with $NaBH_4$ in THF[22] at −30 °C for 15 min gave hemiaminal **15** regio- and chemoselectively, as a separable 11:1 diastereomeric mixture in a combined yield of 82%. Under the Ley conditions ($PhSO_2H$, $CaCl_2$, CH_2Cl_2, rt, 2 h),[19] the diastereomeric mixture of hemiaminal **15** was converted smoothly to sulfone **12** as a separable diastereomeric mixture in 84% yield. Since the subsequent acid-catalyzed α-amidoalkylation reaction is known to pass through the *N*-acyliminium ion[23] intermediate, the diastereomeric mixture of sulfone **12** was used for the next step without separation. We have previously demonstrated that the combination of α-phenylsulfonyllactams as the reactive substrates with *in situ* generated organozinc reagents is efficient for the *trans*-α-amidoalkylation of malimide-derived sulfones, albeit the diastereoselectivities are modest.[24] The application of this method to the asymmetric synthesis of alkaloids has been recently nicely demonstrated by Martin.[25] In the event, the diastereomeric mixture of sulfone **12** in CH_2Cl_2 was treated with the zinc reagent, generated *in situ* from vinyl magnesium bromide and a 1 M solution of anhydrous $ZnCl_2$ in diethyl ether, at rt for 2 h to produce the desired vinylated product 9 in 82% yield as a diastereomeric mixture (dr = 6.8:1). On the basis of the observed small vicinal coupling constant between H_4 and H_5 ($J_{4,5}$ = 2.0 Hz), the stereochemistry of the major diastereomer of **9** was assigned as *trans*.[22] This assignement was confirmed by NOESY experiments on the major diastereomer **9**. The NOE correlations between H_4 and the vinylic proton at C1′, as well as H_5 and a benzylic proton were observed, which indicate the 4,5-*trans*-stereochemistry.

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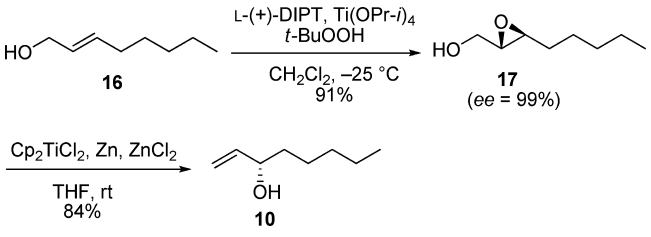
On the other hand, (*S*)-allylic alcohol **10** was synthesized from (*E*)-2-octenol in two steps (Scheme 3). The Sharpless

Scheme 3



asymmetric epoxidation[17] of (*E*)-2-octenol (**16**) gave epoxy alcohol **17** in 91% yield (99% *ee*), which was converted in 84% yield to (*S*)-allylic alcohol **10** by treatment with Cp_2TiCl_2, Zn, and $ZnCl_2$ in THF at rt.[18] To the best of our knowledge, this is the first use of this method for the preparation of the pre-*ω*-chain of PGs. In addition, the easy availability of other achiral (*E*)-allylic alcohols and versatility of both the Sharpless asymmetric epoxidation reaction and the Yadav's method render this method flexible for preparing other analogues of pre-*ω*-chain of PGs.

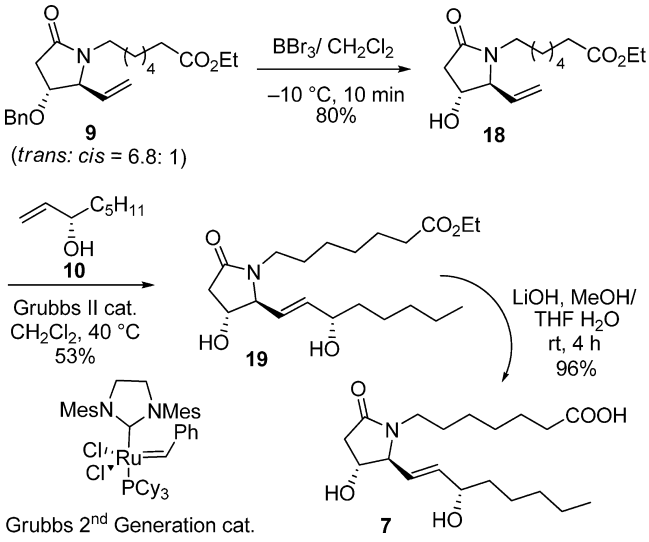
With vinylic compound **9** and allylic alcohol **10** in hand, their cross olefin metathesis reaction was then attempted. However, all the attempts using the Grubbs second generation catalyst[26] were unsuccessful, with the starting vinyl lactam **9** remaining intact.

The failure of cross olefin metathesis might be attributed to the steric hindrance of the substrate **9**. Thus the unprotected *β*-hydroxy-*γ*-lactam **18** was envisioned as the substrate for the cross olefin metathesis reaction. The benzyl group in compound **9** was cleaved chemoselectively by treatment with BBr_3 in CH_2Cl_2 at −10 °C. To our delight, the two alcoholic diastereomers are separable and the major diastereomer **18** was isolated in 80% yield. The subsequent cross olefin metathesis between **18** and allylic alcohol **10** in the presence of the Grubbs second generation catalyst proceeded smoothly in CH_2Cl_2 at 40 °C to produce the desired olefin **19** in 53% yield. The formation of (*E*)-olefins from the cross olefin metathesis reactions has been well documented in the literature.[7e,14d,16] The *E*-geometry of olefin **19** was also deduced from the characteristic olefinic vicinal coupling constant (J_{vic} = 15.4 Hz) and the absorption at 968 cm^{-1} in its IR spectrum. Finally, LiOH-catalyzed saponification of ester **19** gave the 8-aza-PGE_1 (**7**) in 96% yield.

To determine the enantiomeric excess of the product, (*R*)-MTPA-Cl and (*S*)-MTPA-Cl were reacted respectively with compound **18**. The ^1H NMR spectrum of each Mosher ester shows only one diastereomer (according to the signal of OMe: δ = 3.57 for (*R*,*R*)-diastereomer; δ = 3.60 for (*R*,*S*)-diastereomer), which allows us to conclude that the *ee* of compound **18** is higher than 95% (at the limit of the method).

In summary, starting from (*R*)-malic acid, the first synthesis of 8-aza-prostaglandin E_1 (8-aza-PGE_1, **7**) was achieved by a longest linear sequence of eight steps with 17% overall yield. The easy introduction of both the *α*-chain (by malimide formation) and the *ω*-chain (by cross olefin metathesis reaction) makes the method flexible. Importantly, the pre-*ω*-chain (**10**) was synthesized from achiral allylic alcohol (**16**) in only two steps. To the best of our knowledge, this is one of the most convenient and flexible methods for the highly

Scheme 4



enantioselective construction of the *ω*-chain of PGs, which, in combination with the cross olefin metathesis strategy, constitutes a powerful strategy for the synthesis of PGs, prostacyclins and analogues in general.

EXPERIMENTAL SECTION

Ethyl 7-[(3*R*)-hydroxy-2,5-dioxopyrrolidin-1-yl]heptanoate (14). To a 150 mL round-bottom flask equipped with a Dean−Stark apparatus were added successively (*R*)-malic acid (5.04 g, 37.3 mmol), commercially available ethyl 7-aminoheptanoate hydrochloride salt **13** (9.41 g, 44.8 mmol), xylene (94 mL), and triethylamine (10.4 mL, 74.6 mmol). The mixture was stirred and heated to reflux for 8 h. The resulting mixture was diluted with EtOAc (30 mL) and washed successively with water (20 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent:EtOAc/PE = 1:1) to afford compound **14** (10.10 g, yield: 76%) as a colorless oil; $[\alpha]_D^{20}$ +47.7 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3444, 1781, 1702, 1407, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 3H), 1.18−1.28 (m, 4H), 1.41−1.53 (m, 4H), 2.18 (t, *J* = 7.6 Hz, 2H), 2.56 (dd, *J* = 18.0, 4.8 Hz, 1H), 2.97 (dd, *J* = 18.0, 8.4 Hz, 1H), 3.38 (t, 7.4 Hz, 2H), 4.01 (q, *J* = 7.2 Hz, 2H), 4.56 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.75 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 24.4, 26.1, 27.1, 28.3, 33.9, 37.1, 38.5, 60.1, 66.6, 173.7, 174.4, 178.4; HRESIMS calcd for $[C_{13}H_{21}NNaO_5]^+$ (M+Na^+): 294.1312; found: 294.1314.

Ethyl 7-[(3*R*)-benzyloxy-2,5-dioxopyrrolidin-1-yl]-heptanoate (11). To a stirred suspension of compound **14** (4.7 g, 17.38 mmol) and Ag_2O (12.0 g, 52.17 mmol) in EtOAc (30 mL) was added BnBr (8.95 g, 52.4 mmol). The reaction was stirred at room temperature for 3 days in dark. After that, the mixture was filtered through a silica gel pad, and washed with EtOAc (35 mL × 3). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (EtOAc/PE = 1:8) to give compound **11** (5.96 g, yield: 95%) as a colorless oil; $[\alpha]_D^{20}$ +38.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 2934, 1710, 1620, 1542, 1399, 1179, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.28−1.34 (m, 4H), 1.52−1.63 (m, 4H), 2.26 (t, *J* = 7.5 Hz, 2H), 2.62 (dd, *J* = 18.2, 4.1 Hz, 1H), 2.91 (dd, *J* = 18.2, 8.3 Hz, 1H), 3.48 (t, *J* = 7.4 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 4.33 (dd, *J* = 8.3, 4.1 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.96 (d, *J* = 11.7 Hz, 1H), 7.29−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 24.7, 26.4, 27.4, 28.6, 34.2, 36.2, 38.6, 60.2, 72.1, 72.9, 128.18 (2C), 128.22, 128.6 (2C), 136.8, 173.6, 174.2, 175.9; HRESIMS calcd for $[C_{20}H_{27}NNaO_5]^+$ (M+H^+): 384.1781; found: 384.1784.

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Ethyl 7-[(4*R*,5*R*/*S*)-4-benzyloxy-5-hydroxy-2-oxopyrrolidin-1-yl]heptanoate (15). To a cooled (−30 °C) solution of compound **11** (1.13 g, 3.13 mmol) in THF (7.8 mL) was added $NaBH_4$ (0.48 g, 12.52 mmol) in one portion. The resulting suspension was stirred at the same temperature for 15 min. Fifteen mL of saturated aqueous solution of $NaHCO_3$ and brine were added. The resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give hemiaminal **15** as a diastereomeric mixture (0.93 g, yield: 82%, *cis*/ *trans* = 11: 1). A sample of the major diastereomer was obtained by flash chromatography on silica gel (EtOAc/PE= 1:3), which was confirmed to be the *cis*-diastereomer. *cis*-**15** (major diastereomer): colorless oil; $[\alpha]_D^{20}$ −15.2 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3390, 2925, 2855, 1731, 1681, 1453, 1385, 1266, 1183, 1121, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.30−1.38 (m, 4H), 1.49−1.65 (m, 4H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.50 (dd, *J* = 16.8, 5.6 Hz, 1H), 2.55 (dd, *J* = 16.8, 6.6 Hz, 1H), 3.22 (ddd, *J* = 14.0, 8.8, 5.6 Hz, 1H), 3.41 (ddd, *J* = 14.0, 9.2, 6.8 Hz, 1H), 3.52 (d, *J* = 8.1 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 4.08−4.15 (m, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 5.12 (dd, *J* = 8.1, 5.6 Hz, 1H), 7.31−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 24.8, 26.6, 27.6, 28.8, 34.2, 35.9, 40.3, 60.2, 71.9, 72.2, 82.2, 128.0 (2C), 128.4, 128.7 (2C), 136.6, 171.1, 173.8; HRESIMS calcd for $[C_{20}H_{29}NNaO_5]^+$ (M+Na^+): 386.1938; found: 386.1935.

Ethyl 7-[(4*R*,5*S*/*R*)-4-benzyloxy-5-(phenylsulfonyl)-2-oxopyrrolidin-1-yl] heptanoate (12). A suspension of the diastereomeric mixture of compound **15** (1.25 g, 3.4 mmol), freshly prepared benzenesulfinic acid (2.93 g, 20.7 mmol), and $CaCl_2$ (2.27 g, 20.7 mmol) in CH_2Cl_2 (86 mL) was stirred for 2 h at rt under an atmosphere of nitrogen. The reaction was quenched with water and extracted with dichloromethane. The combined extracts were washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent:EtOAc/PE = 1:1) to give a diastereomeric mixture of sulfone compound **12** (1.41 g, yield: 84%) as a colorless oil, which, upon standing at −20 °C for several weeks epimerized to give *trans*-**12** as a single diastereomer. *trans*-**12**: colorless oil; $[\alpha]_D^{20}$ +17.3 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 2859, 1714, 1449, 1407, 1316, 1150, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.18−1.34 (m, 4H), 1.44−1.59 (m, 4H), 2.01 (dd, *J* = 17.8, 6.3 Hz, 1H), 2.20−2.27 (m, 3H), 3.04 (ddd, *J* = 13.7, 7.8, 5.4 Hz, 1H), 3.81 (dt, *J* = 13.7, 7.8 Hz, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 4.32 (d, *J* = 6.3 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.74 (s, 1H), 7.22−7.26 (m, 2H), 7.28−7.36 (m, 3H), 7.55−7.62 (m, 2H), 7.70−7.75 (m, 1H), 7.80−7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.26, 24.73, 25.91, 26.22, 28.59, 34.15, 36.80, 41.91, 60.19, 71.21, 72.63, 82.69, 127.80 (2C), 128.17, 128.59 (2C), 129.15 (2C), 129.82 (2C), 134.99, 135.57, 136.57, 173.61, 173.73; HRESIMS calcd for $[C_{26}H_{33}NNaO_6S]^+$ (M+Na^+): 510.1921; found: 510.1922.

Ethyl 7-[(4*R*,5*S*/*R*)-4-benzyloxy-2-oxo-5-vinylpyrrolidin-1-yl]-heptanoate (9). To a solution of anhydrous zinc chloride (1.0 M in diethyl ether, 2.93 mL. 2.93 mmol) in dichloromethane (6.0 mL) was added dropwise an Et_2O solution of the vinyl magnesium bromide (1.0 M in diethyl ether, 4.9 mL, 4.90 mmol). The mixture was stirred at room temperature under an atmosphere of nitrogen for 30 min. A solution of the diastereomeric mixture of sulfone **12** (1.191 g, 2.44 mmol) in anhydrous dichloromethane (5 mL) was added and the mixture was stirred at room temperature for another 14−16 h. The reaction was quenched with water, and extracted with dichloromethane (3 × 25 mL). The combined organic phases were dried, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (eluent:EtOAc/PE = 1:3−1:1) to give vinyl lactam **9** as an inseparable diastereomeric mixture (896 mg, yield: 82%, *cis*/*trans* = 1:6.8). A sample of pure *trans*-diastereomer (*trans*-**9**) was obtained via *O*-debenzylation-diastereomers separation and re-*O*-benzylation. *trans*-**9**: colorless oil; $[\alpha]_D^{20}$ −16.3 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 2929, 2855, 1735, 1694, 1457, 1179, 1092, 1063, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.21−1.36 (m, 4H), 1.41−1.63 (m, 4H), 2.26 (t, *J* = 7.6 Hz, 2H), 2.46 (dd, *J* = 17.2, 3.2 Hz, 1H), 2.65 (dd, *J* = 17.2, 6.6 Hz, 1H), 2.75−2.85 (m, 1H), 3.61 (dt, *J* = 13.6, 8.0 Hz, 1H), 3.88 (ddd, *J* = 6.6, 3.2, 3.2 Hz, 1H), 4.05 (dd, *J* = 7.8, 3.2 Hz, 1H), 4.11 (q, 7.2 Hz, 2H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 5.24−5.31 (m, 2H), 5.63 (ddd, *J* = 17.6, 9.6, 7.8 Hz, 1H), 7.27−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 24.8, 26.4, 27.0, 28.8, 34.3, 37.0, 40.3, 60.2, 67.2, 71.2, 118.8, 127.6 (2C), 127.9, 128.5 (2C), 135.1, 137.5, 172.3, 173.7; HRESIMS calcd for $[C_{22}H_{31}NNaO_4]^+$ (M+Na^+): 396.2145; found: 396.2149.

Ethyl 7-[(4*R*,5*S*)-4-benzyloxy-2-oxo-5-vinylpyrrolidin-1-yl]-heptanoate (18). To a vigorously stirred solution of the diastereomeric mixture of **9** (*cis*/*trans* = 1:6.8, 60 mg, 0.16 mmol) in CH_2Cl_2 (1.6 mL) was slowly added BBr_3 (1.0 M in CH_2Cl_2, 0.32 mL, 0.32 mmol) at −10 °C under an atmosphere of Ar. The mixture was stirred at the same temperature for 10 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2 (3 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column flash chromatography eluting with ethyl acetate:petroleum ether (2:1) to give diastereomer **18** as a colorless oil (37 mg, yield: 80%). $[\alpha]_D^{20}$ −25.6 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3386, 2921, 1735, 1692, 1449, 1428, 1250, 1179, 1063, 968 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 3H), 1.18−1.26 (m, 4H), 1.36−1.1.46 (m, 2H), 1.47−1.54 (m, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 2.23 (dd, *J* = 17.1, 3.1 Hz, 1H), 2.58 (dd, *J* = 17.1, 6.5 Hz, 1H), 2.74 (ddd, *J* = 14.8, 8.2, 5.5 Hz, 1H), 3.48 (dt, *J* = 14.8, 7.8 Hz, 1H), 3.85 (dd, *J* = 7.9, 2.2 Hz, 1H), 4.02 (q, *J* = 7.2 Hz, 2H), 4.01−4.05 (m, 1H), 4.32 (d, 4.3 Hz, 1H, D_2O exchangeable), 5.10−5.20 (m, 2H), 5.55 (ddd, *J* = 7.9, 9.6, 17.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$); δ 14.0, 24.6, 26.1, 26.7, 28.5, 34.0, 39.3, 40.3, 60.1, 69.8 (2C), 118.4, 134.5, 172.9, 173.7; HRESIMS calcd for $[C_{15}H_{25}NNaO_4]^+$ (M+Na^+): 306.1676; found: 306.1673.

[(2*S*,3*S*)-3-Pentyloxiran-2-yl]methanol (17). Under a nitrogen atmosphere, to a stirring and cooled (−25 °C) suspension of activated powered 4 Å molecular sieves (950 mg) in anhydrous CH_2Cl_2 (60 mL) were added successively L-DIPT (1.10 g, 4.7 mmol) in anhydrous CH_2Cl_2 (5 mL) and $Ti(OPr\text{-}i)_4$ (1.10 g, 3.9 mmol) in anhydrous CH_2Cl_2 (4 mL). The mixture was stirred for 15 min, and commercially available (*E*)-2-octenol (**16**) (2.0 g, 15.6 mmol) in anhydrous CH_2Cl_2 (5 mL) was added. After stirring for 30 min, TBHP (2.20 mL, 21.9 mmol) was added slowly. The mixture was stirred at the same temperature for 5 h before quenching with an aqueous solution (7 mL) containing $FeSO_4$ (2.42 g) and citric acid (760 mg). The mixture was stirred for 15 min. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (15 mL × 3). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/PE = 1:5) to give epoxide **17** (2.05 g, yield: 91%, *ee* = 99%) as a colorless oil. $[\alpha]_D^{20}$ −38.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3427, 2954, 2915, 2859, 1602, 1465, 1374, 1080, 1026, 889 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.9 (t, *J* = 7.0 Hz, 3H), 1.28−1.36 (m, 4H), 1.38−1.49 (m, 2H), 1.54−1.60 (m, 2H), 2.23 (t, *J* = 5.5 Hz, 1H, D_2O exchangeable), 2.92 (dt, *J* = 4.5, 2.5 Hz, 2H), 2.95 (td, *J* = 5.6, 2.3 Hz, 1H), 3.61 (m, 1H), 3.87−3.93 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.5, 25.6, 31.5, 31.5, 56.1, 58.6, 61.8; HRESIMS calcd for $[C_8H_{16}NaO_2]^+$ (M+Na^+): 167.1043; found: 167.1064. The enantiomeric excess (*ee*) of epoxide (2*S*,3*S*)-**17** was determined by HPLC analysis of the corresponding 3,5-dinitrobenzoyl ester (column: Chiralpak AD-H; *n*-hexane/ethanol = 80:20; flow rate: 1.0 mL/min). t_R (min): (2*S*,3*S*)-**17**: 39.0 (99.5%); (2*R*,3*R*)-**17**: 41.3 (0.48%), *ee* = 99% (c.f. Supporting Information).

(*S*)-Oct-1-en-3-ol (10). To a red solution of Cp_2TiCl_2 (9.71 g, 39.0 mmol) in anhydrous THF (45 mL) were added anhydrous zinc chloride (18.6 mL, 0.7 M in Et_2O, 13.0 mmol) and zinc powder (2.50 g, 39 0.0 mmol). The mixture was stirred for 1 h at room temperature while the solution turned green. To the resultant mixture was added epoxide **17** (1.87 g, 13.0 mmol) in anhydrous THF (7 mL), and the resultant mixture was stirred for 30 min. The reaction was quenched with aqueous HCl (1.0 M, 5 mL), and the mixture was extracted with

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Et_2O (10 mL × 3). The organic layers were successively washed with water, 10% aqueous $NaHCO_3$, water, and brine; dried over anhydrous Na_2SO_4; filtered; and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Et_2O/PE = 1:5) to give compound **10** (1.40 g, yield: 84%) as a colorless oil. $[\alpha]_D^{20}$ +10.0 (*c* 1.0, $CHCl_3$); IR (film) ν_{max}: 3423, 2958, 2925, 2851, 1653, 1590, 1348, 1270, 1121, 1080, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.22−1.41 (m, 6H), 1.42−1.55 (m, 2H), 2.00 (d, *J* = 2.4 Hz, 1H, D_2O exchangeable), 4.01−4.09 (m, 1H), 5.05 (dt, *J* = 10.4, 1.3 Hz, 1H), 5.18 (dt, *J* = 17.0, 1.3 Hz, 1H), 5.83 (ddd, *J* = 17.0, 10.4, 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 25.0, 31.8, 37.0, 73.2, 114.4, 141.4; HRESIMS calcd for $[C_8H_{16}NaO]^+$ ($M+Na^+$): 151.1093; found: 151.1086.

Ethyl 7-{(4*R*,5*S*)-4-hydroxy-5-[(3*S*,*E*)-3-hydroxyoct-1-en-1-yl]-2-oxopyrrolidin-1-yl} heptanoate (19). To a stirred solution of compound **18** (45 mg, 0.16 mmol) and compound **10** (100 mg, 0.80 mmol) in CH_2Cl_2 (1.6 mL) was added Grubbs second generation catalyst (27 mg, 0.03 mmol). After being stirred at 40 °C for 24 h, the mixture was concentrated under reduced pressure. The residue was purified by column flash chromatography on silica gel (eluent:EtOAc/PE = 2:1) to give compound **19** as a colorless oil (32 mg, yield: 53%). $[\alpha]_D^{20}$ −7.0 (*c* 0.2, $CHCl_3$); IR (film) ν_{max}: 3375, 2929, 2855, 1739, 1660, 1457, 166, 1179, 968 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.15−1.39 (m, 10H), 1.40−1.55 (m, 4H), 1.55−1.64 (m, 2H), 2.27 (t, *J* = 7.4 Hz, 2H), 2.34 (dd, *J* = 17.0, 3.6 Hz, 1H), 2.69 (dd, *J* = 17.0, 6.4 Hz, 1H), 2.80 (ddd, 14.5, 8.0, 5.6 Hz, 1H), 3.29 (s, 1H, D_2O exchangeable), 3.58 (dt, *J* = 14.5, 8.0 Hz, 1H), 3.87−3.94 (dd, *J* = 8.2, 1.9 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.08−4.16 (m, 2H), 4.28 (br, 1H, D_2O exchangeable), 5.47 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.73 (dd, *J* = 15.4, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.2, 22.6, 24.7, 25.1, 26.2, 26.9, 28.6, 31.6, 34.2, 37.2, 39.4, 40.4, 60.3, 68.9, 70.7, 71.9, 126.9, 138.0, 172.4, 174.0; HRESIMS calcd for $[C_{21}H_{37}NNaO_5]^+$ ($M+Na^+$): 406.2564; found: 406.2564.

7-{(4*R*,5*S*)-4-Hydroxy-5-[(3*S*,*E*)-3-hydroxyoct-1-en-1-yl]-2-oxopyrrolidin-1-yl} heptanoic acid (7). To a solution of compound **19** (98 mg, 0.26 mmol) in a mixture of MeOH/THF/H_2O (2.5 mL, 3/3/ 1) was added LiOH (30 mg, 1.28 mmol) at 0 °C. After being stirred overnight at room temperature, the reaction was quenched with an aqueous solution of HCl (2.0 M), and pH adjusted to 2. The mixture was extracted with EtOAc (3 × 4 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column flash chromatography (eluent: EtOAc) on silica gel to give compound **7** (87 mg, yield: 96%) as a white waxy solid. $[\alpha]_D^{20}$ −12.0 (*c* 0.27, MeOH); IR (film) ν_{max}: 3382, 2925, 2855, 1710, 1664, 1640, 1485, 1387, 1258, 1051, 968 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 0.91 (t, *J* = 6.6 Hz, 3H), 1.27−1.43 (m, 10H), 1.44−1.65 (m, 6H), 2.24 (dd, *J* = 17.2, 2.8 Hz, 1H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.73 (dd, *J* = 17.2, 6.4 Hz, 1H), 2.90 (ddd, *J* = 13.4, 7.8, 5.2 Hz, 1H), 3.54 (dt, *J* = 13.4, 7.8 Hz, 1H), 3.96 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.05−4.13 (m, 2H), 5.51 (dd, *J* = 15.4, 8.2 Hz, 1H), 5.73 (dd, *J* = 15.4, 6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 23.7, 26.0, 26.2, 27.5, 28.0, 29.8, 32.9, 34.8, 38.2, 40.3, 41.6, 71.0, 71.2, 72.6, 127.5, 139.4, 175.3, 177.5; HRESIMS calcd for $[C_{19}H_{32}NO_5]^-$ ($M-H^+$): 354.2286; found: 354.2277.

■ ASSOCIATED CONTENT

Supporting Information

Chiral HPLC chromatogram of 3,5-dinitrobenzoate derivative of compound **17**; NOESY spectral of compound **9**; ^1H and ^{13}C NMR spectra of all new compounds, ^1H NMR spectra of two diastereomeric Mosher esters prepared from (*R*) and (*S*)-MTPA-Cl and compound **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Marks, F.; Furstenberger, G. *Prostaglandins, Leukotrienes and Other Eicosanoids. From Biogenesis to Clinical Application*; Wiley-VCH: Weinheim, 1999.

(2) For a recent review on the chemistry of prostaglandins, see: Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533−1564 and references cited therein..

(3) (a) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847−876. (b) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439−4486.

(4) *J. Chem. Educ.* **2010**, *87*, 1348; http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.

(5) For selected syntheses of 11-deoxy-8-aza-prostaglandin E_1 analogues, see: (a) Smith, R. L.; Lee, T.; Gould, N. P.; Cragoe, E. J., Jr.; Oien, H. G.; Kuehl, F. A., Jr. *J. Med. Chem.* **1977**, *20*, 1292−1299. (b) Barco, A.; Benetti, S.; Pollini, G. P. *J. Org. Chem.* **1979**, *44*, 1734−1736. (c) Wang, C.-L. *J Tetrehedron Lett.* **1982**, *23*, 1067−1070. (d) Zoretic, P. A.; Bhakta, C.; Jardin, J. *J. Heterocyclic Chem.* **1983**, *20*, 465−466 and references cited therein..

(6) Jones, R. L.; Giembycz, M. A.; Woodward, D. F. *Br. J. Pharmacol.* **2009**, *158*, 104−145 and references cited therein..

(7) For representative novel and efficient strategies, see: (a) Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799−11805. (b) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841−5842. (c) Schrader, T. O.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 10998−11000. (d) Jacobo, S. H.; Chang, C.-T.; Lee, G.-J.; Lawson, J. A.; Powell, W. S.; Pratico, D.; FitzGerald, G. A.; Rokach, J. *J. Org. Chem.* **2006**, *71*, 1370−1379. (e) Sheddan, N. A.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3101−3104. (f) Coulthard, G.; Erb, W.; Aggarwal, V. K. *Nature* **2012**, *489*, 278−281. (g) Hayashi, Y.; Umemiya, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450−3452.

(8) For a review on recent developments in the synthesis of prostaglandins and analogues, see: (a) Das, S.; Chandrasekhar, S.; Yadav, J. S.; Gree, R. *Chem. Rev.* **2007**, *107*, 3286−3337. For selected recent examples on the synthesis of bioactive analogues of PGs, see: (b) Jahn, U.; Dinca, E. *J. Org. Chem.* **2010**, *75*, 4480−4491. (c) Patel, P.; Lee, G. J.; Kim, S.; Grant, G. E.; Powell, W. S.; Rokach, J. *J. Org. Chem.* **2008**, *73*, 7213−7218.

(9) (a) Billot, X.; Chateauneuf, A.; Chauret, N.; Denis, D.; Greig, G.; Mathieu, M. C.; Metters, K. M.; Slipetz, D. M.; Young, R. N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1129−1132. (b) Young, R. N.; Billot, X.; Han, Y.; Slipetz, D. A.; Chauret, N.; Belley, M.; Metters, K.; Mathieu, M. C.; Greig, G. M.; Denis, D.; Girard, M. *Heterocycles* **2004**, *64*, 437−446.

(10) Cameron, K. O.; Lefker, B. A.; Chu-Moyer, M. Y.; Crawford, D. T.; Jardine, P. D.; DeNinno, S. L.; Gilbert, S.; Grasser, W. A.; Ke, H.; Lu, B.; Owen, T. A.; Paralkar, V. M.; Qi, H.; Scott, D. O.; Thompson, D. D.; Tjoa, C. M.; Zawistoski, M. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1799−1802.

(11) (a) Kambe, T.; Maruyama, T.; Nakai, Y.; Oida, H.; Maruyama, T.; Abe, N.; Nishiura, A.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2012**, *20*, 3502−3522. (b) Kambe, T.; Maruyama; Nakai, Y.; Yoshida, H.; Oida, Hi.; Maruyama, T.; Abe, N.; Nishiura, A.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2012**, *20*, 2235−2251. (c) Arns, S.; Gibe, R.; Moreau, A.; Morshed, M. M.; Young, R. N. *Bioorg. Med. Chem.* **2012**,

20, 2131−2140. (d) Kambe, T.; Maruyama, T.; Nagase, T.; Ogawa, S.; Minamoto, C.; Sakata, K.; Maruyama, T.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2012**, *20*, 702−713. (e) Kambe, T.; Maruyama, T.; Nakano, M.; Nakai, Y.; Yoshida, T.; Matsunaga, N.; Oida, H.; Konaka, A.; Maruyama, T.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2012**, *20*, 396−401. (f) Nair, S. K.; Matthews, J. J.; Cripps, S. J.; Ma, C.-R.; Dovalsantos, E. Z.; Grubbs, A. W.; Sach, N. W.; Hoeve, W. T.; Koster, H.; Flahive, E. J.; Tanis, S. P.; Renner, M.; Wiltenburg, J. V. *Tetrahedron Lett.* **2010**, *51*, 1451−1454. (g) 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*, 6124−6127. (h) Elworthy, T. R.; Kertesz, D. J.; Kim, W.; Roepel, M. G.; Quattrocchio-Setti, L.; Smith, D. B.; Tracy, J. L.; Chow, A.; Li, F.; Brill, E. R.; Lach, L. K.; Mcgee, D.; Yang, D. S.; Chiou, S. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1655−1659.

(12) Togo, S.; Chen, H.-C.; Takahashi, T.; Kubota, T.; Matsuo, K.; Morioka, D.; Watanabe, K.; Yamamoto, H.; Nagashima, Y.; Shimada, H. *J. Surg. Res.* **2008**, *146*, 66−72.

(13) Haubrich, D. R.; Cruet, J. P.; Reid, W. D. *Br. J. Pharmacol.* **1973**, *48*, 80−87.

(14) (a) Huang, S.-Y.; Chang, Z.; Tuo, S.-C.; Gao, L.-H.; Wang, A.-E; Huang, P.-Q. *Chem. Commun.* **2013**, *49*, 7088−7090. (b) Huo, H.-H.; Xia, X.-E.; Zhang, H.-K.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 455−465. (c) Luo, S.-P.; Guo, L.-D.; Gao, L.-H.; Li, S.; Huang, P.-Q. *Chem.—Eur. J.* **2013**, *19*, 87−91. (d) Fu, R.; Ye, J.-L.; Dai, X.-J.; Ruan, Y.-P.; Huang, P.-Q. *J. Org. Chem.* **2010**, *75*, 4230−4243.

(15) Hu, K.-Z.; Ma, J.; Qiu, S.; Zheng, X.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 1790−1801.

(16) For a review on the recent developments in olefin cross-metathesis, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

(17) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976 and references cited therein..

(18) Yadav, J. S.; Shekharam, T.; Gadgil, V. R. *J. Chem. Soc., Chem. Commun.* **1990**, 843−844.

(19) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. *Tetrahedron* **1991**, *47*, 1311−1328.

(20) Bhat, K. L.; Flanagan, D. M.; Joullié, M. M. *Synth. Commun.* **1985**, *15*, 587−598 and references cited therein..

(21) Zheng, J.-L.; Liu, H.; Zhang, Y.-F.; Zhao, W.; Tong, J.-S.; Ruan, Y.-P.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2011**, *22*, 257−263.

(22) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949−4952.

(23) For recent reviews on α-amidoalkylation via *N*-acyliminium ions, see: (a) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339−368. (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513−541.

(24) Huang, P.-Q.; Tang, X.; Chen, A.-Q. *Synth. Commun.* **2000**, *13*, 2259−2268.

(25) David, G. W.; Richard, W. H., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523−3525.

(26) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.