Synthesis of a Highly Selective EP2-Receptor Agonist

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Received 17 November 2001

Abstract: A practical method for the synthesis of the prostanoid EP2-receptor agonist **1** was developed. This method includes magnesium-mediated Julia olefination of aldehyde **2** with the optically active sulfone **3**, which was prepared from allylic alcohol **4** using the Sharpless asymmetric epoxidation procedure.

Key words: prostaglandins, asymmetric synthesis, Julia olefination, magnesium, EP2-receptor agonist

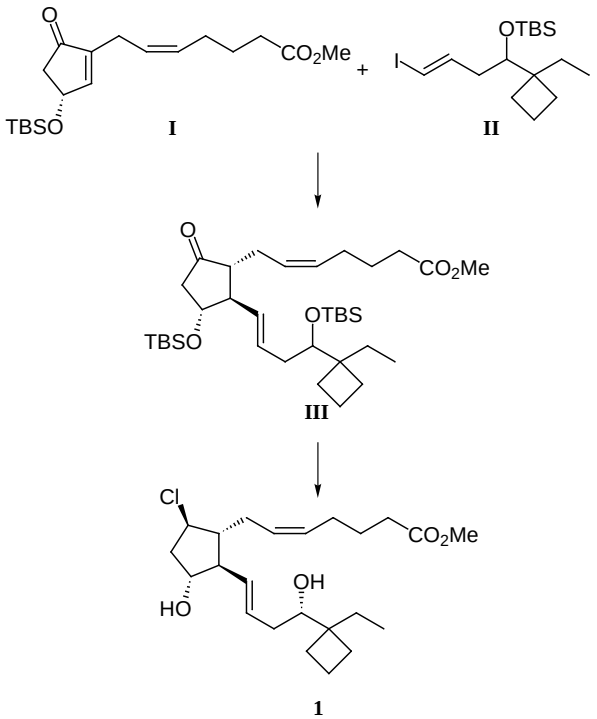
In preceding publications,[1] we reported the development of the highly selective EP2-receptor agonist **1**, which demonstrates a high affinity for the EP2-receptor of mouse (m) and human (h). Also in functional studies, **1** showed nearly 10 and 1000 fold higher potency than the reported selective ligands butaprost[2] and AH-13205,[3] respectively, in stimulating cAMP production in the cells expressing mEP2-receptor (Table). The EP2-receptor agonist **1** also showed nearly the same affinity as PGE_2 for the EP2-receptor, and suppressed the spontaneous uterine motility in anesthetized rats in late-term pregnancy.[1a,c] These findings suggest that **1** is a promising candidate of tocolytic with a new mechanism of action for clinical use. The information mentioned above prompted us to develop a practical synthetic method for the newly discovered EP2-receptor selective agonist **1**. According to the reported method[1c] described in Scheme 1, the undesired 16(*R*)-isomer of **1** has to be removed by column chromatography on silica gel, while this laborious procedure should be successfully avoided by this new synthesis (Scheme 2). Additionally, removal of the $\Delta^{8,9}$-olefinic by-product, which was formed in the chlorination reaction, was found to be easier with this method. We report here the improved synthesis, which includes enantioselective introduction of 16-OH by an asymmetric epoxidation and a stereoselective construction of a 13,14-*trans*-double bond by magnesium-mediated Julia olefination.[4]

Enantioselective Synthesis of 3: As shown in Scheme 2, the highly selective EP2-receptor agonist **1** can be synthesized by Julia olefination of **2** with **3**. Enantioselective synthesis of **3** is outlined in Scheme 3. Asymmetric epoxidation of the allylic alcohol **4**, which was prepared by reducing the corresponding α,β-unsaturated ethyl ester[5] with diisobutylaluminum hydride, afforded **5**. Regioselec-

Table Biological Profile of **1**.

	Binding K_i (nM)[a]				EC_{50} (nM)[b]
Compounds	mEP1	mEP2	mEP3	mEP4	mEP2
1	> 10^4	3.3	> 10^4	6100	3.8
PGE_2	18	38	5.0	3.1	2.0
Butaprost	> 10^4	790	> 10^4	> 10^4	26
AH-13205	2800	320	49	2200	2500

[a] Using membrane fractions of Chinese hamster ovary (CHO) cells expressing the mouse prostanoid receptors (mEP1, mEP2, mEP3 and mEP4), K_i values were determined by the competitive binding assay, which was performed according to the method of Kiriyama et al.[15] with some modifications. When the test compound did not displace binding of radioligands by 50% even at a concentration of 10^4 nM, the K_i value was not determined (expressed > 10^4).
[b] With regard to the subtype-receptor agonistic activity, EC_{50} values were determined based on the effect of the test compounds on the increase in the intracellular cAMP production in the mouse EP2 receptor.

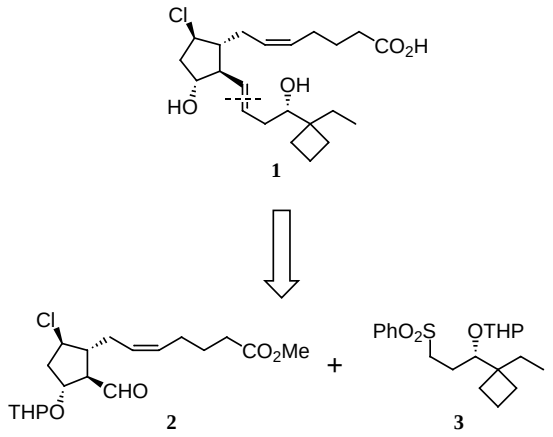


Scheme 1 The reported synthesis of **1**

Synlett 2002, No. 1, 01 02 2002. Article Identifier:
1437-2096,E;2002,0,02,0239,0242,ftx,en;Y22301ST.pdf.

ISSN 0936-5214

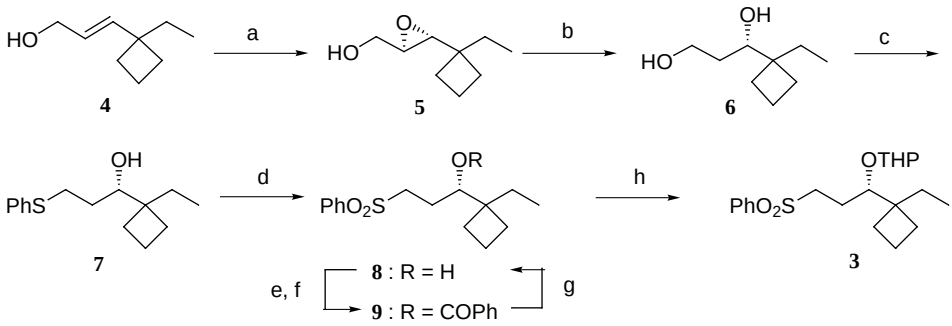
tive ring opening of epoxide **5** with sodium bis(methoxyethoxy)aluminum hydride gave **6**. Selective monotosylation of the primary alcohol **6**, followed by the S_N2 reaction under phase transfer conditions, gave the sulfide **7**[6], oxidation of which with Oxone® afforded sulfone **8**. For purification, **8** was converted to the benzoate **9** prior to recrystallization. After recrystallization from ethanol, **9** was again converted to **8**[7] (optical purity 99% ee), protection of which as a tetrahydropyranyl ether yielded **3**.[8]



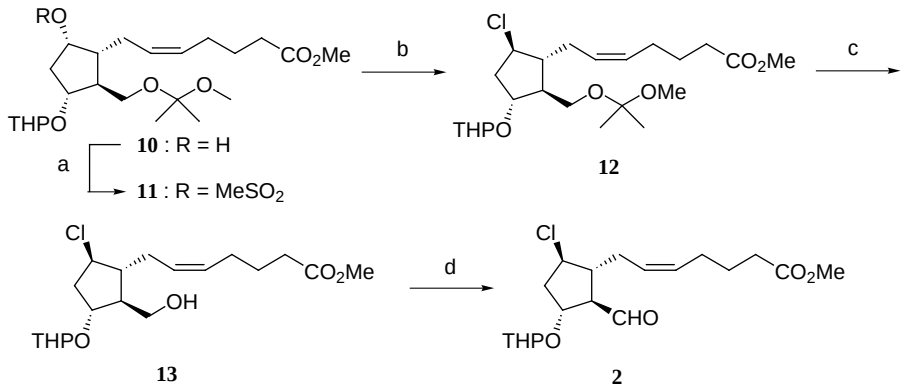
Scheme 2 Retrosynthesis of **1**

Synthesis of 2: Preparation of the aldehyde **2** from an optically active intermediate **10**[9] is outlined in Scheme 4. Methanesulfonation of **10**, which is easily available from the Corey lactone,[9,10] afforded **11**. Substitution reaction of the 9α-methanesulfonate **11** with tetrabutylammonium chloride gave a 9β-chloro derivative **12**[11] and a $\Delta^{8,9}$-olefinic by-product. The ratio of the 9β-Cl to the olefinic by-product was approximately 5.4:1. After selective deprotection of the 1-methyl-1-methoxyethyl group,[9] compound **13** and the $\Delta^{8,9}$-olefinic derivative could be easily separated by column chromatography on silica gel. Oxidation of **13** with a sulfur trioxide-pyridine complex in dimethyl sulfoxide and triethylamine gave the aldehyde **2**.[12]

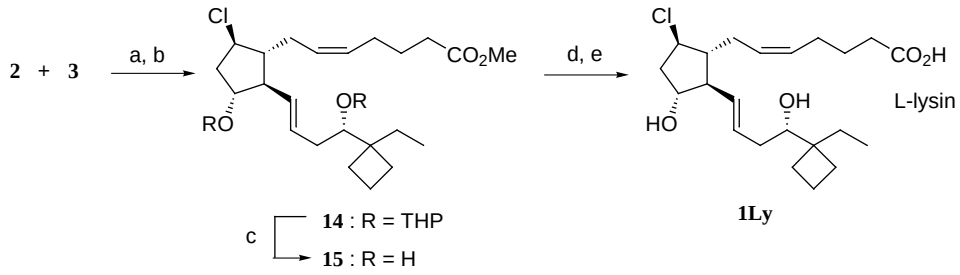
Julia olefination of 2 with 3: Synthesis of **1** and its L-lysine salt **1Ly** is outlined in Scheme 5. Julia olefination of **2** with **3**,[13] followed by acidic deprotection of THP groups, gave **15** and the corresponding 13(*Z*) isomer (*E*/*Z* = 5/1). The *Z* isomer could be easily removed by column chromatography on silica gel. Compound **15** was converted to **1** by alkaline hydrolysis with sodium hydroxide. Addition of L-lysine to a solution of **1** in ethanol, followed by dilution with ethyl acetate, afforded the crystalline salt **1Ly** in good yield. As shown in the Figure, absolute configuration of the 16-OH of **1Ly** was finally determined by X-ray analysis.[14]



Scheme 3 Synthesis of the optically active ω chain unit **3**. *Reagents*: (a) *t*-BuOOH, Ti(*i*-PrO)$_4$, D-(–)-DIPT, CH_2Cl_2, –20 ºC; (b) Na(MeOCH$_2$CH$_2$O)$_2$AlH$_2$, toluene (95% from **4**); (c) TsCl, *n*-Bu$_4$NBr, NaOH$_{aq}$, toluene, then PhSH (99%); (d) Oxone®, MeOH, H_2O (quant.); (e) PhCOCl, DMAP, pyridine then recrystallized from EtOH (71%); (f) NaOHaq, MeOH (quant.); (g) DHP, *p*-TsOH, CH_2Cl_2 (96%).



Scheme 4 Synthesis of the aldehyde **2**. *Reagents*: (a) MsCl, Et_3N, CH_2Cl_2; (b) *n*-Bu$_4$NCl, Et_3N, toluene, 60 ºC; (c) HCl$_{aq}$, THF (61% from **10**); (d) SO_3-pyridine, Et_3N, DMSO (quant.).



Scheme 5 Synthesis of **1** and **1Ly.** *Reagents*: (a) *n*-BuLi, THF, –78 ºC; (b) Mg (powdered, -50 mesh), TMSCl, MeOH (47% from **3**); (c) *p*-TsOH, MeOH (78%); (d) $NaOH_{aq}$, MeOH (81%); (e) L-lysine, EtOH, EtOAc (91%).

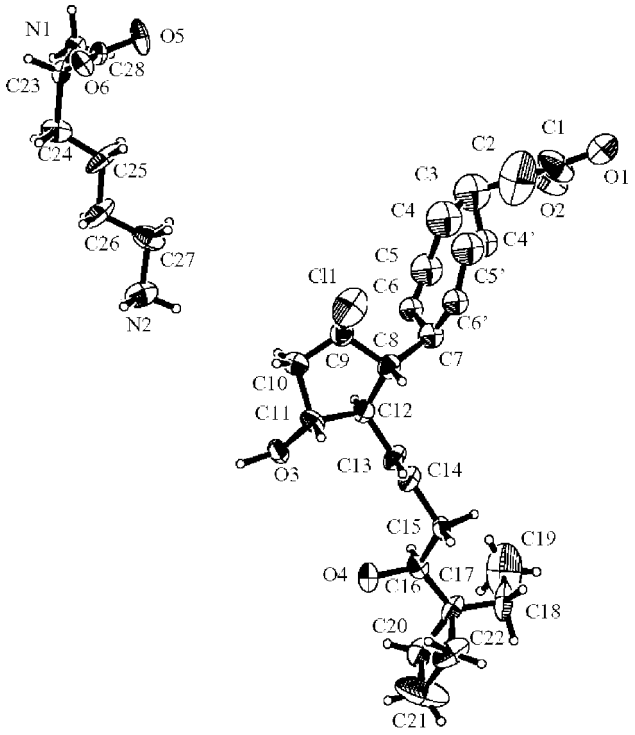


Figure X-ray crystallographic structure of **1Ly**[14]

In summary, we have succeeded in developing a practical synthesis of the highly selective EP2-receptor agonist **1**, which was converted to the crystalline L-lysine salt **1Ly** demonstrating excellent physicochemical properties such as good crystalline property, good water-solubility and so on. In the process, a Julia olefination of aldehyde **2**, prepared from **10**, with the optically active sulfone **3**, prepared from the optically active epoxide **5**, was included as a key reaction (Scheme 2).

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(5) The α,β-unsaturated ester was prepared by Horner–Emmons reaction of triethyl phosphono acetate with 2,2-(trimethylene)butanal, the preparation of which was described in ref.[1b] of this report.

(6) Spectrum data of compound **7**: IR(neat): 3441, 2962, 1584, 1481, 1439, 1310, 1272, 1071, 1026, 737, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.10 (m, 5 H), 3.80–3.65 (m, 1 H), 3.28–2.94 (m, 2 H), 2.00–1.20 (m, 11 H), 0.88 (t, *J* = 7.5 Hz, 3 H); TLC: R_f = 0.52 (*n*-hexane/AcOEt = 4:1).

(7) Spectrum data of compound **8**: IR(neat): 3525, 2963, 2936, 2878, 1447, 1304, 1148, 1087, 1072, 748, 689, 599, 533 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.00–7.90 (m, 2 H), 7.70–7.50 (m, 3 H), 3.66–3.55 (m, 1 H), 3.50–3.10 (m, 2 H), 2.00–1.30 (m, 11 H), 0.88 (t, *J* = 7.5 Hz, 3 H); TLC: R_f = 0.32 (*n*-hexane/AcOEt = 2:1). The optical purity of compound **8** was determined based on the result of HPLC analysis of its benzoyl derivative **9**.

(8) Spectrum data of compound **3**: IR(neat): 2939, 2864, 1446, 1305, 1150, 1075, 1031, 987 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.00–7.90 (m, 2 H), 7.70–7.50 (m, 3 H), 4.40 (m, 1 H), 3.94–3.70 (m, 1 H), 3.62–3.28 (m, 3 H), 3.17–3.04 (m, 1 H), 2.24–1.20 (m, 16 H), 0.85 (t, *J* = 7.4 Hz, 3 H); TLC: R_f = 0.42 and 0.37 (*n*-hexane/AcOEt = 4:1).

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(12) Spectrum data of compound **2**: IR(neat): 2947, 2868, 2736, 1439, 1352, 1323, 1247, 1201, 1154, 1133, 1077, 1034, 1021, 970 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 9.76 and 9.73 (2 × d, *J* = 2.0 Hz, 1 H), 5.60–5.30 (m, 2 H), 4.65–4.50 (m, 2 H), 4.15–3.95 (m, 1 H), 3.90–3.70 (m, 1 H), 3.67 (s, 3 H), 3.60–3.40 (m, 1 H), 2.80–1.40 (m, 18 H); TLC: R_f = 0.60 (*n*-hexane/AcOEt = 2/1).

(13) **Typical Experimental Procedure for the Synthesis of 14 from 2 and 3**: To a stirred solution of **3** (19.8 g, 54.0 mmol) in dry THF (125 mL) was added *n*-butyllithium (1.6 M in

hexane, 33.8 mL, 54.0 mmol) at –78 ºC under an argon atmosphere. The reaction mixture was stirred for 1 h at –78 ºC and then added to a stirred solution of **2** (16.0 g, 41.5 mmol) in 125 mL of dry THF (125 mL) at –78 ºC. After stirring for 1 h at –78 ºC, the resulting mixture was treated with acetic anhydride (7.85 mL, 83.0 mmol) and allowed to warm up to ambient temperature over 1 h. The reaction mixture was treated with sat. aq ammonium chloride and extracted with EtOAc repeatedly. The combined organic layers were washed with water, then brine, dried over anhyd magnesium sulfate, and concentrated in vacuo to afford a crude acetoxy sulfone (40.1 g) as a dark-brown viscous oil. TLC: R_f = 0.41 (*n*-hexane/EtOAc = 3:1); IR(neat): 2943, 2863, 1740, 1447, 1371, 1307, 1228, 1150, 1131, 1075, 1031 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.00–7.45 (m, 5 H), 5.70–5.20 (m, 2 H), 5.00–3.20 (m, 14 H), 2.60–1.20 (m, 37 H), 1.10–0.80 (m, 3 H).

To a stirred solution of the crude acetoxy sulfone (10.6 g, 11.0 mmol) in 100 mL of methanol was added powdered magnesium (-50 mesh, 2.40 g, 100 mmol) under an argon atmosphere. The mixture was again stirred (15 min), and a catalytic amount of chloro trimethylsilane (0.1 mL) was added. After stirring for 1 h at ambient temperature, the reaction mixture was poured into ice-cold aq ammonium chloride and extracted with EtOAc. The organic layer was washed with water, then brine, dried over anhyd magnesium sulfate, and concentrated in vacuo to afford a crude oil, which was purified by column chromatography on silica gel to give a mixture of 13*E*- (compound **14**) and 13*Z*-olefinic compounds (3.0 g, 47% yield from aldehyde **2**) as a pale yellow oil (*E*/*Z* = 5:1). The undesired *Z* isomer was easily removed by silica gel column chromatography after deprotection. TLC: R_f = 0.66 (*n*-hexane/EtOAc = 3:1); IR(neat): 2942, 2875, 1741, 1440, 1352, 1200, 1115, 1077, 1032, 977 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 5.80–5.25 (m, 4 H), 4.60 (m, 2 H), 4.15–3.75 (m, 4 H), 3.57 (s, 3 H), 3.55–3.35 (m, 3 H), 2.50–1.40 (m, 34 H), 1.00–0.85 (m, 3 H).

(14) X-Ray analysis (Figure)of the salt **1Ly** consisting of a 1/1 molar ratio of **1** and L-lysine was conducted. The absolute configuration of the 16-OH was determined to be an *S*-form based on its configuration relative to the absolute configuration of L-lysine in the crystal lattice. Lattice Parameters: a = 32.91(2) Å, b = 5.91(2) Å, c = 17.64(2) Å, β = 112.52(6)° V = 3169(10) $Å^3$. Space Group: C2. Cu-Kα radiation (λ = 1.54178 cm^{-1}) graphite monochromated was used for data collection. 1307 Reflections with $I > 3\sigma(I)$ was used for final structure factor calculations. $R = \Sigma||Fobs|-|Fcalc||/\Sigma|Fobs| = 0.104$. $Rw = ((\Sigma w(|Fobs|-|Fcalc|)^2/\Sigma wFobs^2)^{1/2} = 0.119$, where $w = 1/\sigma^2(Fobs)$.

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