Efficient Asymmetric Synthesis of Prostaglandin E1

Jae-Chul Junga and Oee-Sook Pakb
a Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, P.O. Box 1848, University, Mississippi 38677-1848, USA
b Department of Chemistry, College of Natural Sciences, Chungbuk National University, Cheongju 361-763, Chungbuk, South Korea

Reprint requests to Dr. Oee-Sook Park. Fax: +82-43-267-2279. E-mail: ospark@cbnu.ac.kr


A simple synthesis of prostaglandin E1 (PGE1) is described. The key steps are an asymmetric Michael addition to establish the desired (R)-configurations at C8 and C12 of the 2-(trimethylsilyl)ethoxymethyl- (SEM) protected PGE1 and its one-pot deprotection with magnesium bromide in high yield. This method is potentially useful for the preparation of other modified prostaglandins.

Key words: Prostaglandin, Asymmetric Michael Addition, Cuprates, Deprotection

Introduction

Prostaglandin and its analogues have important functions in the animal body and a variety of biological effects [1]. Many naturally occurring prostaglandins as well as many artificial forms have been synthesized by several groups [2]. The major approaches to the synthesis of prostaglandins fall into three categories (Fig. 1). Key steps in the original approach included a Wittig reaction of aldehyde 2 and triphenylphosphane (3), followed by a Wittig-Horner reaction to furnish the C13–C14 E-olefin partial structure of prostaglandins [3]. Another strategy employed Michael addition reactions of ester 5 and allylic alcohol 6 [4]. In an alternative approach, the Noyori reaction of cyclopentenone 7 with allylic alcohol 6 and Z-allylic iodide 8 readily generated prostaglandins, which is the most elegant synthetic method in the area of three component coupling [5].

Since the first isolation of prostaglandins, numerous synthetic methods have been developed [6]. Most of these routes are based on two or three component coupling reactions. Recently, Feringa reported an enantioselective synthesis using a tandem 1,4-addition aldol reaction to a cyclopentene-3,5-dione monoaclatal [7]. Florent generated a chiral amino-cyclopentenone moiety via [3,3] sigmatropic rearrangement and palladium-catalyzed cross-coupling followed by a ring closing metathesis (RCM) reaction [8].

During our studies of asymmetric Michael addition reactions of cyclopentenones, we realized that a more efficient method of preparing prostaglandin E1 (PGE1, 1) and its analogues was needed. Herein, we describe an efficient synthesis of prostaglandin E1 (1) via asymmetric Michael addition employing 2-(trimethylsilyl)ethoxymethyl (SEM) protecting groups.

Results and Discussion

Synthesis of fragments 13 and 14 required the development of a method for preparing tert-butyldimethylsilyl (TBS) or SEM-protected ethers 10 and 11 in excellent yields (Scheme 1). These were ac-
Fig. 1. General synthetic approaches to prostaglandins.

Scheme 2. Synthesis of prostaglandin E₁ (1).

complished by subjecting commercially available (S)-(-)-1-octyn-3-ol (9) to TBS or SEM protection. Fragment 13 was smoothly prepared from TBS-ether 10 which underwent hydroboration with catecholborane in benzene in 80% yield [9]. E-Vinylstannane 14 was obtained from SEM-ether 11 through hydrostan-

nation with tributyltin hydride (Bu₃SnH) in the presence of 2,2′-azo-bis-isobutynitrile (AIBN) as an ini-
tiator in 70% yield [10]. Bis-protection of the commercially available chiral hydroxyl acid 16 [11] with 2 equiv. of SEM-Cl in the presence of lithium carbonate (Li₂CO₃) and 4-(dimethylamino)pyridine (DMAP)
gave SEM-cyclopentenone 17. Asymmetric Michael addition of 17 with E-vinylstannane 14 [12] in the presence of n-BuLi at −78 ℃ in THF gave fully protected SEM-ester 18 in 67% yield. However, treatment of 17 with vinylborane 13 was unsatisfactory, and for the most part, the starting material was recovered. Finally, treatment of fully protected SEM-ester 18 with magnesium bromide and nitromethane in the presence of 1-butanol was unsatisfactory, and for the most part, the starting material was recovered. The reaction mixture was allowed to cool to r. t. The crude product was purified by flash column chromatography (silica gel, 3% EtOAc/hexanes) to afford SEM-ether 11 (0.5 g, 98%) as a colorless oil. \( R_f = 0.4 \) (3% ethyl acetate in hexanes).

\[ [\alpha]_D^{25} = -128.3 \text{ (c = 1.1, CHCl}_3) \] – IR (neat, NaCl); \( \nu = 3312, 2954, 2894, 1647, 1249, 1024, 836 \text{ cm}^{-1}. \) – \( ^1\text{H NMR} \) (CDCl\(_3\), 500.14 MHz): \( \delta = 4.93 \) (d, J = 6.8 Hz, 1H, OCH\(_2\)O), 4.67 (d, J = 6.8 Hz, 1H, OCH\(_2\)O), 4.33 (t, J = 6.4 Hz, 1H, CH\(_3\)), 3.70 (q, J = 10.4 Hz, 1H, CH\(_3\)), 2.44 (brs, 1H, CH\(_2\)), 1.75 – 1.69 (m, 2H, CH\(_2\)), 1.50 – 1.41 (m, 2H, CH\(_2\)), 1.34 – 1.26 (m, 4H, 2 \times \text{CH}_2), 1.00 – 0.92 (m, 2H, CH\(_2\)), 0.89 (t, J = 6.8 Hz, 3H, CH\(_3\)), 0.01 (s, 9H, SiMe\(_3\)). – \( ^{13}\text{C NMR} \) (CDCl\(_3\), 125.67 MHz): \( \delta = 92.4 \) (OCH\(_2\)O), 82.5 (CH), 81.0 (CH), 79.9 (CH), 65.0 (CH\(_2\)), 31.8 (CH\(_2\)), 24.9 (CH\(_2\)), 22.6 (CH\(_2\)), 18.1 (CH\(_2\)), 14.0 (CH\(_3\)), 1.4 (SiMe\(_3\)), 3C. – HRMS: \( m/z = 257.1944 \) (calcld. 257.1937 for Cl\(_{14}\)H\(_{20}\)O\(_2\)Si, [M+H]\(^+\)).

\((S)\)-3-(2-Trimethylsilyloxyethoxymethyl)-1-tributylstannyl-1- octene (14)

To a stirred solution of acid 11 (0.51 g, 2.0 mmol), tributyltin hydride (0.88 g, 3.0 mmol) and 2,2’-azo-bis(isobutyronitrile (4 mg, 0.024 mmol) were added under argon atmosphere and kept for 1 h at 120 ℃. The reaction mixture was allowed to cool to r. t. The crude product was purified by flash column chromatography (silica gel, 1% EtOAc/hexanes) to afford E-vinylstannane 14 (0.77 g, 70%) as a pale yellow oil. \( R_f = 0.4 \) (1% ethyl acetate in hexanes): – \( [\alpha]_D^{25} = -83.0 \) (c = 0.6, CHCl\(_3\)). – IR (neat, NaCl); \( \nu = 2956, 2873, 1464, 1377, 1249, 1054, 836 \text{ cm}^{-1}. \) – \( ^1\text{H NMR} \) (CDCl\(_3\), 500.14 MHz): \( \delta = 6.11 \) (d, J = 19.2 Hz, 1H, CH\(_3\)), 5.78 (dd, J = 7.2, 18.8 Hz, 1H, CH=CH), 4.68 (dd, J = 6.8, 6.8 Hz, 2H, OCH\(_2\)O), 4.00 – 3.95 (m, 1H, CH\(_3\)), 3.80 – 3.73 (m, 1H, CH\(_2\)), 3.56 – 3.49 (m, 1H, CH\(_2\)), 1.66 – 1.55 (m, 2H, CH\(_2\)), 1.52 – 1.43 (m, 6H, 3 \times \text{CH}_2), 1.38 – 1.25 (m, 12H, 6 \times \text{CH}_2), 1.00 – 0.81 (m, 20H, 4 \times \text{CH}_2, 4 \times \text{CH}_2), 0.04 (s, 9H, SiMe\(_3\)). – \( ^{13}\text{C NMR} \) (CDCl\(_3\), 125.67 MHz): \( \delta = 148.5 \) (CH=CH), 131.1 (CH=CH), 91.8 (OCH\(_2\)O), 79.9 (CH\(_3\)), 65.0 (CH\(_2\)), 53.5 (CH\(_2\)), 31.8 (CH\(_2\)), 29.1 (3 \times \text{CH}_2, 3C), 27.4 (3 \times \text{CH}_2, 3C), 25.2 (CH\(_2\)), 22.7 (CH\(_2\)), 18.1 (CH\(_2\)), 14.1 (CH\(_3\)), 13.7 (3 \times \text{CH}_3, 9C), 9.5 (3 \times \text{CH}_3, 3C), –1.4 (SiMe\(_3\), 3C). – HRMS: \( m/z = 549.3158 \) (calcld. 549.3150 for C\(_{26}\)H\(_{57}\)O\(_2\)Si, [M+H]\(^+\)).

2-Trimethylsilyloxyethyl-(R)-(1-(2-trimethylsilyloxyethoxymethoxy))-5-oxo-1-cyclopentene-1-heptanoate (17)

To a stirred solution of acid 16 (0.23 g, 1.0 mmol) in dry DMF (3 mL) were added DMAP (3 mg, 0.02 mmol) and lithium carbonate (0.16 g, 2.2 mmol) under argon atmosphere at 10 ℃, followed by addition of SEM-Cl (0.37 g, 2.2 mmol) at that temperature. The reaction mixture was stirred at r. t. for 20 h. The reaction mixture was diluted with ether (10 mL) and washed with water (5 mL) and...
brine (5 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 15 % EtOAc/hexanes) to afford SEM-cyclopentenone 17 (0.15 g, 31 %) as a pale yellow oil. Rf = 0.4 (15 % ethyl acetate in hexanes). – [α]D²⁰ = −4.0 (c = 0.2, CHCl₃). – IR (neat, NaCl): ν = 2951, 1740 (CO), 1715 (COO), 1408, 1249, 1032, 837 cm⁻¹. – 1H NMR (CDCl₃, 500.14 MHz): δ = 7.18 (s, 1H, CH=CH), 5.27 (s, 2H, OCH₂), 4.78 (d, J = 20.5 Hz, 2H, OCH₂), 3.71 – 3.61 (m, 4H, 4 × 2H, OCH₂), 4.80 (d, J = 11.5 Hz, 2H, OCH₂), 1.67 – 1.59 (m, 2H CH₂), 1.53 – 1.46 (m, 2H, CH₂), 1.37 – 1.31 (m, 4H, 4 × CH₂), 0.96 (t, J = 8.4 Hz, 4H, 4 × SiCH₃), 0.03 (s, 9H, SiMe₃), 0.02 (s, 9H, SiMe₃). – 13C NMR (CDCl₃, 125.67 MHz): δ = 205.9 (CO), 173.3 (COO), 154.4 (CH), 148.3 (C), 94.5 (CH₂), 88.7 (CH₂), 73.6 (CH), 67.8 (CH₂), 65.5 (CH₂), 42.7 (CH₂), 34.3 (CH₂), 29.0 (CH₂), 28.8 (CH₂), 27.2 (CH₂), 24.7 (CH₂), 24.5 (CH₂), 18.1 (CH₂), 18.0 (CH₂), −1.2 (SiMe₃, 3C), −1.4 (SiMe₃, 3C). – HRMS: m/z = 487.2903 (caled. 487.2911 for C₂₂H₄₄O₆Si₂, [M+H⁺]).

Preparation of 2-thienyl(cyano)copper lithium (12, 2-ThCuCNLi)

To a stirred solution of thiophene (1.56 g, 20.4 mmol) in THF (10 mL) n-BuLi (12.5 mL, 20.0 mmol; 1.6 M solution in hexane) was added at −78 °C under argon atmosphere, and stirring was continued at −78 °C for 30 min. The mixture was transferred to a slurry of copper cyanide (1.8 g, 20.0 mmol) −hexane) was added at −78 °C for 30 min, and quenched with 10 % aqueous NH₂OH solution (2 mL) and saturated aqueous NH₄Cl solution (3 mL). The mixture was warmed to r.t., diluted with ether (10 mL) and washed with brine (5 mL). The organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20 % ether/hexanes) to afford fully protected SEM ester 18 (0.1 g, 67 %) as a pale yellow oil. Rf = 0.3 (20 % ether in hexanes). – [α]D²⁰ = +30.7 (c = 1.2, CHCl₃). – IR (neat, NaCl): ν = 2951, 1740 (CO), 1716 (COO), 1463, 1249, 1105, 1031, 836 cm⁻¹. – 1H NMR (CDCl₃, 500.14 MHz): δ = 6.96 (dd, J = 5.0, 3.8 Hz, 1H, CH=CH), 6.80 (dd, J = 0.8, 3.4 Hz, 1H, CH=CH), 5.29 (s, 2H, OCH₂O), 5.28 (s, 2H, OCH₂O), 4.80 (d, J = 2.4 Hz, 2H, OCH₂O), 4.74 (d, J = 7.2 Hz, 1H, CH), 3.74 – 3.67 (m, 6H, 3 × CH₂), 3.66 – 3.60 (m, 1H, CH), 2.81 (ddd, J = 6.8, 6.4, 6.0 Hz, 2H, CH₂, CH₂), 2.40 – 2.28 (m, 4H, CH₂, CH₂), 2.03 (t, J = 11.5 Hz, 2H, CH₂), 1.67 – 1.59 (m, 4H, 2 × CH₂), 1.56 – 1.47 (m, 4H, 2 × CH₂), 1.40 – 1.28 (m, 8H, 4 × CH₂), 1.01 – 0.93 (m, 9H, 3 × CH₂, CH₃), 0.05 (s, 3H, SiMe₃), 0.04 (s, 6H, SiMe₃), 0.04 (s, 9H, SiMe₃), 0.03 (s, 9H, SiMe₃). – 13C NMR (CDCl₃, 125.67 MHz): δ = 206.0 (CO), 173.5 (COO), 154.5 (CH=CH), 148.6 (CH=CH), 94.7 (CH₂), 93.7 (CH₂), 89.0 (CH₂), 84.9 (CH), 78.7 (CH), 73.7 (CH), 68.0 (CH₂), 65.8 (CH₂), 65.4 (CH₂), 51.6 (CH₂), 42.9 (CH₂), 34.5 (2 × CH₂, 2C), 29.3 (CH₂), 29.2 (CH₂), 29.1 (CH₂), 29.0 (CH₂), 27.7 (CH₂), 27.5 (CH₂), 26.2 (CH₂), 24.9 (CH₂), 24.7 (CH₂), 18.3 (CH₂), 18.2 (2 × CH₂, 2C), −1.2 (3 × SiMe₃, 9C). – HRMS: m/z = 745.4932 (caled. 745.4926 for C₃₈H₇₆O₈Si₃, [M+H⁺]).

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