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Preparation of the Major Urinary Metabolite of (-)-Prostaglandin E₂

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Abstract

The best way to measure whole body production of the locally acting hormone prostaglandin E₂ (PGE₂) is to assess the accumulation of the major urinary metabolite, PGE₂ U_M. A practical preparation of this delicate diacid is described. This synthetic PGE₂U_M will enable production of the antibodies that will be used to quantify this key metabolite.

Introduction

Prostaglandin E₂ (**1**) (Eq. 1) displays a wide array of biological activity.¹ Recently, it was observed that some lung cancers are associated with an elevated production of PGE₂.² The best way to measure whole body production of the locally acting hormone is to assess the accumulation of the major urinary metabolite, PGE₂ U_M (**2**). We had reported the preparation of the ethyl ester **3** of racemic PGE₂U_M.³ We now describe a practical preparation of the enantiomerically pure diacid **2**, requisite for the production of the PGE₂U_M antibodies that will be used to quantify this key metabolite.

(1)

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Supplementary Data Available. General experimental procedures, experimental procedures and spectra for all new compounds can be found in the online version.

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Result and Discussion

For the preparation of **2** (Eq. 2), there were three problems to be addressed: improvement of the production of the racemic allylic alcohol **4** having the alkyl substituents *trans* on the cyclopentane ring, resolution⁴ of **4**, and the conversion of the enantiomerically pure acetate **R-5** to (-)-PGE₂U_M**2**. Throughout, we had to be mindful of the sensitivity of the easily-dehydrated β -hydroxy ketone.

(2)

The starting materials for the synthesis of **4** were, as before,^{3a} the diazo ketone **8** and the diene aldehyde **12** (Scheme 1). As previously, the diazoketone **8** was prepared by Michael addition of benzoylacetone to ethyl acrylate, to give diketone **7**. The diketone **7** was smoothly converted⁵ to the diazo ketone **8** on exposure to *p*-nitrobenzenesulfonyl azide (*p*-NBSA) and DBU.

We have made several improvements in the preparation of the diene aldehyde **12**. Ozonolysis of cyclohexene followed by overnight (vs. 45 min) exposure to triethylamine and EtOH⁶ led to ethyl 6-oxohexanoate **9** in better yield (78% vs 45%). Wittig reaction of the phosphonium salt **10** with the replacement of 1 equiv KHMDS (original) with *t*-BuOK proceeded smoothly to give the 6*E*, 8*Z*-dienol **11** with a similar improvement (82% vs 46%). Oxidation of **11** with 15 mol equiv MnO₂, which is less expensive than the Dess-Martin periodinane previously used, delivered the dial **12** with a slightly improved yield (86% vs 81%).

With the two components **8** and **12** in hand, we used the original procedure to prepare the aldol product **16** (Scheme 2). Condensation of the potassium enolate of the diazoketone **8** with the dial **12** in the presence of triethylchlorosilane (TESCl) in toluene gave the TES-protected aldol **13** together with the free aldol product **14**. Several other bases were tried, but without positive results. The recovered dial was found to be an *E/Z* and *E/E* mixture, so it could not be recycled. Removal of the TES group from the protected aldol product **13** with TBAF in THF delivered an additional quantity of the free aldol product **14**. Silylation of the combined lots of **14** with TBSCl led to the desired cyclization precursor **15**.

The diazoketone **15** was cyclized with catalytic rhodium octanoate in CH₂Cl₂ to provide the bicyclic ketones **16** and **17** in a ratio of 65:35. We were not able to separate these two substances by chromatography, so we developed an improved protocol for preparing pure **16**. We found that while the alcohol from reduction of **16** had about the same TLC *R_f* as **16** itself, the alcohol from reduction of **17** was much more polar. Further, **17** appeared to be significantly more reactive toward Dibal than was **16**. Thus, reduction of the mixture of **16** and **17** with a limited

amount of DIBAL led to total reduction of **17** to its alcohol, which was easily separated. The recovered mixture of **16** and its derived alcohol was then oxidized to give pure **16**.

We then addressed the opening of the cyclopropyl ketone **16** in the presence of the TBS group. In the past,³ we had run the opening at low temperature, to be able to isolate the kinetic product from ring opening, having the two alkyl substituents *cis* on the cyclopentane ring. To our delight, we found that allowing the reaction mixture to warm to -30 to -10 °C for 6 h gave the pure free *trans* thioether **19** and some free bicyclic ketone **18**, that could be recycled with TBSCl to **16**. Silylation of **19** gave **20**, that on oxidation and Mislow rearrangement⁷ gave the desired racemic allylic alcohol **4**.

We had planned to effect the resolution of **4** by acetylation with the (*R*)-selective Amano lipase AK and vinyl acetate **21**. In the past,⁴ we have observed that such acetylations produce high ee acetate initially, but were sometimes difficult to drive to completion. It was therefore important in the synthesis design to have a *Z* alkene in **20** and its precursors, so that Mislow rearrangement would give the diastereomer **4**, such that the enantiomer of **4** having the *R* alcohol at C-15 would have the same ring absolute configuration as the natural prostaglandins. That way, the high ee acetate **R-5** initially produced could be carried on directly to the enantiomerically pure urinary metabolite **2**. The success of this approach was confirmed by the optical rotation of the final product **2**.

We initially planned (Scheme 4) to convert (*R*)-**5** to the diacid **2** by reduction of the ketone to the alcohol, saponification, and oxidation of the diacid diol so prepared to the diacid diketone. The preparation of the diacid diol **22** was successful, but we were not able to find conditions for the purification of the derived diacid diketone. We found it more practical to alkylate the diacid with benzyl bromide, leading to the bis benzyl ester **23**. Oxidation⁸ of **23** proceeded smoothly to give the enone **24**.

The β-hydroxy ketone **25** was quite sensitive, quickly deteriorating in CDCl₃. Nevertheless, deprotection of **24** with HF in pyridine was sufficiently mild to deliver intact **25**. Hydrogenation then completed the synthesis of (-)-PGE₂U_M**2**.

There had been three previous syntheses of (-)-**2**, by groups at Lilly,^{9a} at Merck^{9b} and at Upjohn.^{9c} Our observed [α]_D = -9.1 (EtOH) agreed well with the reported^{9a} [α]_D = -8 (EtOH). The ¹H NMR of our synthetic **2** was also congruent with those previously observed.⁹

Conclusion

We have developed a practical stereoselective synthetic approach to the major urinary metabolite of (-)-prostaglandin E₂. This synthesis has made this metabolite available in sufficient quantity to allow continuation of the ongoing physiological studies.

Experimental

Diethyl (13*S**)-(14*E*)-(1,2,3,4-Tetranor)-9-oxo-11-hydroxy-13-phenylthio-Δ¹⁴-prostanedioate **19**

To a stirred solution of the bicyclic ketone **16** (118 mg, 0.244 mmol) and thiophenol (81 mg, 0.733 mmol) in CH₂Cl₂ (2.5 mL) at -78 °C was added a solution of BF₃·OEt₂ (139 mg, 2.13 mmol) in CH₂Cl₂ (0.5 mL) over 5 min. The mixture was maintained at -30 to -10 °C for an additional 6 h. The reaction mixture was partitioned between CH₂Cl₂ and, sequentially, saturated aqueous NaHCO₃ and brine. The organic extract was dried (Na₂SO₄) and concentrated, and the residue was chromatographed to afford the free thioether **19** (60 mg, 51% yield from **16**) as a colorless oil; TLC *R*_f (MTBE/ petroleum ether = 1/1) = 0.24; ¹H NMR δ

7.44-7.47 (m, 2H), 7.27-7.30 (m, 3H), 5.35-5.48 (m, 2H), 4.36 (q, 1H, $J = 6.8$ Hz), 4.21 (dd, 1H, $J = 5.2$ and 9.6 Hz), 4.13 (m, 4H), 3.14 (bs, 1H), 2.71 (dd, 1H, $J = 7.2$ and 18.4 Hz), 2.42-2.51 (m, 1H), 2.11-2.42 (m, 7H), 1.93-2.03 (m, 1H), 1.81-1.85 (m, 1H), 1.63-1.67 (m, 1H), 1.43-1.48 (m, 2H), 1.21-1.27 (m, 6H), 1.07-1.19 (m, 2H); ^{13}C NMR δ u: 10 215.9, 173.9, 173.2, 133.7, 60.43, 60.40, 47.0, 33.9, 31.3, 28.6, 26.9, 25.3, 24.5; d: 133.9 (2), 132.7, 128.9 (2), 127.9, 127.4, 70.9, 53.0, 50.3, 48.6, 14.2 (2); IR (film) 3467, 2931, 1729, 1374, 1179 cm^{-1} ; ESI MS (m/z), 499.2 ($\text{M}^+ + \text{Na}$); HRMS calcd for $\text{C}_{26}\text{H}_{36}\text{O}_6\text{SNa}$ 499.2130 found 499.2126. Further elution gave the free bicyclic ketone **18** (22 mg, 24% yield from **16**) as a colorless oil, TLC R_f (MTBE/petroleum ether = 1/1) = 0.11. The analytical data for **18** were found to be identical to those previously reported.

Diethyl (13S*)-(14E)-(1,2,3,4-Tetranor)-9-oxo-11-dimethyl(dimethylethyl)silyloxy-13-phenylthio- Δ^{14} -prostanedioate **20**

To a stirred solution of thioether **19** (84 mg, 0.18 mmol) in CH_2Cl_2 (1.5 mL) was added imidazole (34 mg, 0.53 mmol) and TBSCl (53 mg, 0.35 mmol), then DMAP (3 mg, cat) at room temperature. After an additional 30 h, the mixture was partitioned between CH_2Cl_2 and H_2O . The organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to afford the TBS-protected thioether **20** (79 mg, 76% yield from **19**) as a colorless oil; TLC R_f (MTBE/petroleum ether = 3/7) = 0.58; ^1H NMR δ 7.34-7.36 (m, 2H), 7.18-7.20 (m, 3H), 5.27-5.34 (m, 2H), 4.40 (q, 1H, $J = 1.6$ Hz), 4.00-4.06 (m, 4H), 3.94 (dd, 1H, $J = 6.0$ Hz and 10.4 Hz), 2.54 (dd, 1H, $J = 6.0$ Hz and 18.0 Hz), 2.31-2.38 (m, 2H), 2.07-2.17 (m, 5H), 1.91-1.97 (m, 2H), 1.63-1.72 (m, 1H), 1.50-1.60 (m, 1H), 1.32-1.39 (m, 2H), 1.14-1.17 (m, 6H), 1.01-1.11 (m, 1H), 0.84-0.96 (m, 1H), 0.81 (s, 9H), 0.04 (s, 3H), 0.01 (s, 1H); ^{13}C NMR δ u: 217.1, 173.4, 173.0, 134.0, 60.3, 60.2, 47.4, 34.0, 31.8, 28.4, 27.1, 26.0, 24.5, 17.8; d: 133.9 (2), 132.5, 128.9 (2), 127.8, 127.6, 71.2, 54.1, 49.4, 48.4, 25.7 (3), 14.25, 14.22, -4.4, -4.7; IR (film) 2933, 2858, 1737, 1180, 836 cm^{-1} ; ESI MS (m/z), 613.3 ($\text{M}^+ + \text{Na}$); HRMS calcd for $\text{C}_{32}\text{H}_{50}\text{O}_6\text{SSiNa}$ 613.2995 found 613.2990.

Diethyl (15R*)-(1,2,3,4-Tetranor)-9-oxo-11-dimethyl(dimethylethyl)silyloxy-15-acetoxyprostanedioate **4**

To a stirred solution of the thioether **20** (154 mg, 0.26 mmol) in CH_2Cl_2 (12 mL) at -78°C was added a solution of 3-chloroperoxybenzoic acid (90 mg, 0.52 mmol) in CH_2Cl_2 (2.0 mL) over a period of 10 min. The mixture was stirred for an additional 50 min, then a solution of trimethyl phosphite (324 mg, 2.61 mmol) in EtOH (4 mL) was added. The mixture was stirred at -78°C for an additional 10 min and then the cooling bath was removed and the mixture was stirred for an additional 6.5 h at room temperature. The mixture was partitioned between EtOAc and, sequentially, saturated aqueous NaHCO_3 and brine. The organic extract was dried (Na_2SO_4) and concentrated, and the residue was chromatographed to afford the allylic alcohol **4** (132 mg, 99% yield from **20**) as a colorless oil; TLC R_f (MTBE/petroleum ether = 1/1) = 0.18; ^1H NMR δ 5.64 (dd, $J = 6.8$ Hz and 15.2 Hz), 5.50 (dd, $J = 8.4$ Hz and 15.2 Hz), 4.05-4.12 (m, 4H), 4.00 (q, 1H, $J = 8.4$ Hz), 2.61 (ddd, 1H, $J = 1.2$ Hz, 7.2 Hz and 18.4 Hz), 2.32-2.52 (m, 3H), 2.27 (t, 2H, $J = 7.6$ Hz), 2.16 (dd, 1H, $J = 8.8$ Hz and 18.0 Hz), 1.87-2.02 (m, 3H), 1.77-1.81 (m, 1H), 1.58-1.65 (m, 2H), 1.36-1.56 (m, 3H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR δ u: 214.9, 173.7, 173.2, 60.5, 60.2, 47.2, 36.7, 34.2, 31.7, 25.0, 24.8, 23.4, 18.0; d: 136.7, 131.0, 72.7, 72.1, 54.5, 52.7, 25.7 (3), 14.24, 14.22, -4.6, -4.7; IR (film) 3467, 2933, 1736, 1101, 838 cm^{-1} ; HRMS: calcd for $\text{C}_{26}\text{H}_{46}\text{O}_7\text{SiNa}$ 521.2911 found 521.2908.

Resolution of racemic allylic alcohol **4**

To a stirred solution of racemic alcohol **4** (230 mg, 0.46 mmol) in vinyl acetate **21** (11 mL) was added R-selective Amano lipase AK (1.8 g). The reaction mixture was stirred at 55°C (oil bath) for an additional 48 h. The suspension was filtered through a pad of celite with MTBE,

and the filtrate was concentrated and chromatographed to afford the acetate **R-5** (87 mg, 70% based on the *R*-allylic alcohol charged) and recovered alcohol **4** (125 mg, 54% based on the racemic allylic alcohol) as colorless oils. For **R-5**: TLC R_f (MTBE/petroleum ether = 1/1) = 0.59; $[\alpha]_D$ -4.9 (c 0.83, CH₂Cl₂); ¹H NMR δ 5.52-5.63 (m, 2 H), 5.22-5.29, 4.04-4.12 (m, 4 H), 4.00 (q, 1 H), 2.61 (ddd, 1 H, J = 1.2 Hz, 7.2 Hz and 18.4 Hz), 2.31-2.43 (m, 3 H), 2.26 (t, 3 H, J = 7.6 Hz), 2.16 (dd, 1 H, J = 8.8 Hz and 18.4 Hz), 1.98-2.03 (m, 4 H), 1.85-1.89 (m, 1 H), 1.75-1.78 (m, 1 H), 1.57-1.65 (m, 4 H), 1.28-1.40 (m, 2 H), 1.20-1.24 (m, 6 H), 0.84 (s, 9 H), 0.01 (s, 6 H); ¹³C NMR δ u: 214.5, 173.4, 173.0, 170.2, 60.3, 60.2, 47.1, 34.11, 34.06, 24.73, 24.70, 23.3, 18.0 d: 133.1, 131.7, 72.7, 72.5, 54.5, 52.6, 25.7 (3), 21.2, 14.24, 14.21, -4.7, -4.8; IR (film) 2935, 1735, 1373, 1240, 840 cm⁻¹; ESI MS (m/z), 563.3 (M⁺+Na); HRMS: calcd for C₂₈H₄₈O₈SiNa 563.3016 found 563.3012.

Dibenzyl (1,2,3,4-Tetranor)-9,15-dioxo-11-dimethyl(dimethylethyl)silyloxyprostanedioate **24**

To stirred solution of acetate **R-5** (21.2 mg, 0.039 mmol) in ethanol (1 mL) was added NaBH₄ (2.2 mg). After an additional 40 min, the reaction mixture was partitioned between EtOAc and H₂O. The organic extract was dried (Na₂SO₄) and concentrated to afford the crude mixture of diastereomeric alcohols.

To a stirred solution of the crude diols in THF (1 mL) was added a 1 M solution of aqueous LiOH (1 mL, 1 mmol) at room temperature. After stirring for 24 h, the mixture was acidified with 1 M aqueous HCl to pH = 3~4, and partitioned between CHCl₃ and saturated brine. The organic extract was dried (Na₂SO₄) and concentrated to afford the bisacid crude **22**.

The crude diacid **22** was dissolved in DMF (1 mL), then powdered K₂CO₃ (39 mg, 0.28 mmol) and benzyl bromide (48 mg, 0.14 mmol) were added. After stirring for 24 h, the reaction mixture was partitioned between EtOAc and H₂O. The organic extract was dried (Na₂SO₄) and concentrated, and the residue was chromatographed to afford the bisbenzyl ester **23** (12.1 mg, 50% yield for 3 steps from the acetate **R-5**). TLC R_f (MTBE/petroleum ether = 1/1) = 0.28 and 0.19; ¹H NMR (diastereomeric mixture, typical signal peaks were recorded) δ 7.31-7.36 (m, 10 H), 5.30-5.53 (m, 2 H), 5.10-5.11 (m, 4 H), 3.94-4.04 (m, 3 H).

To a stirred solution of the bisbenzyl ester **23** (12.1 mg, 0.019 mmol) in CH₂Cl₂ (1 mL) was added Dess-Martin periodinane (33 mg, 0.078 mmol) at room temperature. After an additional 30 min, the mixture was concentrated and the residue was chromatographed to afford the desired enone **24** (9.5 mg, 40% yield from **R-5**) TLC R_f (MTBE/petroleum ether = 1/1) = 0.77. $[\alpha]_D$ -34.7 (c 0.45, CH₂Cl₂); ¹H NMR δ 7.31-7.37 (m, 10H), 6.69 (dd, 1H, J = 15.6 and 8.8 Hz), 5.11 (s, 2H), 5.09 (s, 2H), 4.09 (q, 1 H, J = 8.4 Hz), 2.67 (ddd, 1H, J = 0.8 Hz, 7.2 Hz and 18.4 Hz), 2.44-2.57 (m, 5H), 2.47-2.49 (m, 2H), 2.14-2.28 (m, 2H), 1.78-1.96 (m, 2H), 1.65-1.67 (m, 4H), 0.85 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ¹³C NMR δ u: 213.5, 198.9, 173.2, 172.7, 135.9 (2), 66.3, 66.2, 47.1, 40.3, 34.1, 31.4, 24.5, 23.4, 23.3, 18.0 d: 144.8, 132.2, 128.6 (4), 128.3 (3), 128.22 (2), 128.20, 72.2, 54.5, 52.4, 25.6 (3), -4.65, -4.74; IR (film): 2932, 1738, 1162, 838, 744 cm⁻¹; ESI MS (m/z), 643.2 (M⁺+Na); HRMS: calcd for C₃₆H₄₈O₇SiNa 643.3067 found 643.3056.

Dibenzyl (1,2,3,4-Tetranor)-9,15-dioxo-11-hydroxyprostanedioate **25**

To a stirred solution of enone **24** (9.5 mg, 0.015 mmol) in CH₃CN (1 mL) at 0 °C was added pyridine (0.1 mL) and 52% solution of HF in H₂O (0.2 mL). After stirring for 7 h, the reaction mixture was mixed with silical gel, concentrated and the residue was chromatographed to afford the free enone **25** (6.5 mg, 84% yield from the enone **24**) TLC R_f (MTBE/petroleum ether = 4/1) = 0.27; $[\alpha]_D$ +11.2 (c 0.25, CH₂Cl₂); ¹H NMR δ 7.31-7.38 (m, 10 H), 6.72 (dd, 1 H, J = 8.4 Hz and 15.6 Hz), 6.31 (d, 1 H, J = 15.6 Hz), 5.11 (s, 2 H), 5.09 (s, 2 H), 4.19 (q, J = 8.4 Hz), 2.79 (ddd, J = 0.8 Hz, 7.2 Hz and 18.4 Hz), 2.44-2.60 (m, 5 H), 2.20-2.41 (4 H), 1.81-1.97

(m, 2 H), 1.65-1.68 (m, 5H); ^{13}C NMR δ u: 212.8, 199.2, 173.4, 172.7, 135.9, 135.8, 66.4, 66.3, 46.0, 40.5, 33.9, 31.3, 24.3, 23.4, 23.2; d: 144.2, 132.4, 128.6 (4), 128.3 (3), 128.2 (3), 71.5, 54.3, 53.0; IR (film): 3464, 2928, 1733, 1453, 1163 cm^{-1} ; HRMS: calcd for $\text{C}_{30}\text{H}_{34}\text{O}_7\text{Na}$ 529.2202 found 529.2198.

(1,2,3,4-Tetranor)-9,15-dioxo-11-hydroxy-13,14-dihydroprostanedioic Acid (PGE_2U_M) 2

To a stirred solution of enone **25** (4.3 mg, 0.0085 mmol) in ethanol (1 mL) was added Pd-C (40 mg). An H_2 balloon was attached, and the mixture was stirred at rt for 40 min. The reaction mixture was filtered and concentrated to give the desired PGE_2U_M **2** (2.5 mg, 90% yield from the enone **25**). TLC R_f ($\text{Et}_2\text{O}/0.5\text{ M pH} = 4$ aqueous buffer/ $\text{HOAc} = 90/9/1$) = 0.14; $[\alpha]_D -9.1$ (c 0.10, MeOH); ^1H NMR (CD_3OD) δ 3.98 (q, 1H, $J = 6.4\text{ Hz}$), 2.57-2.67 (m, 3H), 2.46-2.48 (m, 2H), 2.32-2.40 (m, 2H), 2.23 (bs, 2H), 2.08 (dd, 1H, $J = 18.0\text{ Hz}$ and 6.8 Hz), 1.70-1.84 (m, 5 H), 1.55-1.59 (m, 5 H); ^{13}C NMR δ u: 217.4, 211.6, 176.3, 175.9, 45.9, 41.4, 38.9, 33.4, 26.9, 25.7, 25.1, 23.9 d: 71.5, 52.0, 47.9; IR (film): 3441, 1703, 1406 cm^{-1} ; HRMS: calcd for $\text{C}_{16}\text{H}_{24}\text{O}_7\text{Na}$ 351.1420 found 351.1414.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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10. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as “d” and for methylene and quaternary carbons as “u”.

SCHEME 1.

SCHEME 2.

SCHEME 3.

SCHEME 4.