established. Although nominal reduction of 1,6-dienes occurs utilizing the current protocol, further studies designed to optimize the organometallic catalyst by both "ligand tuning" and "metal tuning" are expected to resolve this problem.

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Supplementary Material Available: Complete experimental details and spectral data for all of the cyclization reactions described herein (38 pages). Ordering information is given on any current masthead page.

Novel and Versatile Strategy for the Synthesis of Prostanoids in the E, F, H, and I Series[§]

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Prostaglandins (PGs) exist in most mammalian tissues.¹ Isolation of PGs from natural biosynthetic sources cannot meet their medicinal demand.² Total synthesis thus remains the only means by which sufficient quantities of prostanoids can be made available.^{2,3} Herein we report a novel biomimetic, cascade-type synthesis⁴ of various prostanoids via common 11α , 9α -epoxyimino-PGHs (i.e., 25 and 27).

Scheme I shows our four-step synthesis of alkenyl aldehyde 9 from the monomethyl ester of azelaic acid (1). The key step 2 \rightarrow 7 involved a [3,3]-sigmatropic rearrangement,⁵ by which two contiguous chiral centers were established. In the conversion of 8 to 9, we were able to reduce a tertiary amide selectively in the presence of a C=C and two ester functionalities to an aldehyde in 50% yield by using MeOTf and L-Selectride in sequence.6

We then condensed this readily available aldehyde (9) with PhNHOH in the presence of 5A molecular sieves to give the corresponding alkenyl nitrone 13 (Scheme I). Various temperatures (105-180 °C) were used for the thermolysis of nitrone 13 in situ to give [3 + 2] cycloadducts, isoxazolidines 15 and 17, in 54-75% overall yields. At 180 °C with 1,2-dichlorobenzene as the solvent, the cyclization took only 4 min and gave isoxazolidines 15 and 17 in a ratio of 1:1.

We elongated the ω -chain of 15 to give enone 21 through the procedures shown in Scheme II. For the synthesis of prostanoids

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Scheme I^a



^aa: (1) SOCl₂, 80 °C; (2) Me₂NH, H₂O (87%). b: (1) LiNH₂, a. (1) $SO(1_2, 00 C, (2) Mc_2(11, 120 (07.0))$. (1) $E1(11_2, 100 M)$ NH₃, Et₂O; (2) $Br(CH_2)_3C(OMe)_3, -33 \ ^{\circ}C (84\%).^{18,19}$ c: $CrO_3, 4.0$ M H₂SO₄ (aq), Me₂CO, room temperature (83%). d: (COCl)₂, Me₂NH, room temperature (87%). e: (1) MeOTf, CH₂Cl₂, room temperature; (2) cis-LiOCH₂CH=CHCH₂OSiPh₂Bu', THF, Δ (for 2 \rightarrow 7, 69%; for 6 \rightarrow 10, 72%).³ f: (1) *n*-Bu₄NF, THF; (2) Ac₂O, Et₃N, room temperature (98%). g: (1) MeOTf, CH₂Cl₂, room temperature; (2) L-Selectride, THF, -78 °C; (3) H₃O⁺ (for $8 \rightarrow 9$, 50% for $11 \rightarrow 12$, 64%).⁶ h: (1) *n*-Bu₄NF, THF; (2) (PhCO)₂O, Et₃N, room temperature (98%). i: PhNHOH, 5A molecular sieves, solvent. j: Δ .⁴

15 and 16

in optically active form, enone 21 was reduced asymmetrically with (S)-BINAL-H^{7,8} to give diastereomeric allylic alcohols (-)-25 (36% yield, 86% e.e.) and (+)-28 (38% yield, 78% e.e.) in 74% overall yield. Saponification of (-)-25 with NaOH in MeOH provided (-)-11 α ,9 α -epoxyimino-PGH₁ sodium salt 26 in 88% vield.

An efficient method for the conversion of epoxyimino-PGH (-)-25 to $(-)-PGE_1$ is appealing because PGEs possess therapeutic value⁹ and can be further converted to PGA, PGB, and PGC.³ Thus we oxidized^{10,11} (-)-25 with *m*-CPBA to afford PGE_1 ester (-)-30 in 65% yield (Scheme II). Finally, a total synthesis of (-)-PGE₁ was accomplished by saponification of ester (-)-30 with bakers' yeast.12

To demonstrate the versatility of 11α , 9α -epoxyimino-PGHs as a common precursor for other types of PGs, we also degraded (-)-25 to a prostanoid in the F series (Scheme II). Thus reductive

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^aa: KOH, MeOH (for $15 \rightarrow 19$, 82%; for $16 \rightarrow 22$, 88%). b: DMSO, (COCl)₂, Et₃N, CH₂Cl₂, -60 °C (for $19 \rightarrow 20$, 93%; for $22 \rightarrow$ **23**, 92%). c: $(MeO)_2P(=O)CHNaC(=O)-n-C_5H_{11}$, DME, 0 °C (for $20 \rightarrow 21, 92\%$; for $23 \rightarrow 24, 88\%$).²⁰ d: (S)-BINAL-H, THF, -100 to $-78 \text{ °C}^{7.8}$ (for $21 \rightarrow (-)-25$ (36%) + (+)-28 (38%); for $24 \rightarrow (+)-27$ (39%) + (-)-29 (41%)). e: NaOH, H₂O, MeOH (88%). f: (1) m-CPBA, CH₂Cl₂, 0 °C; (2) NH₄Cl, H₂O (for (-)-25 → (-)-30, 65%).^{10,11} g: Zn, HOAc, 55 °C (for (-)-25 → (+)-32, 89%; for (+)-27 → (+)-33, 88%).¹³⁻¹⁵ h: Bakers' yeast, 0.1 M phosphate buffer, pH 7.0 (72%).²¹ i: PdCl₂(MeCN)₂, LiCl, MeCN (70%).¹

cleavage of the N–O bond in (-)-25 with Zn dust and glacial acetic acid¹³⁻¹⁵ gave an 89% yield of 9α -anilino-PGF₁ (+)-32 ([α]²⁵_D +25.8° (c 0.37, THF)).

Prostacyclin (i.e., PGI) and its analogues are difficult synthetic targets but have great medicinal potential.9 Results from our AM1 calculation¹⁶ indicated that the PGI₂ enamine analogue was ~ 0.81 kcal/mol more stable than the parent enol ether toward hydrolysis.

We planned to synthesize a 6.9α -anilino-PGI₂ via an epoxyimino-PGH intermediate. Thus we converted 4-pentyn-1-ol (3) to γ -alkenyl aldehyde 12 in six steps (Scheme I). Then we treated 12 with PhNHOH and 5A molecular sieves in bromobenzene to form nitrone intermediate 14. This solution was then immersed in a preheated oil bath at 170 °C for 6 min to afford bicyclic isoxazolidines 16 (40%) and 18 (35%) in 75% overall yield.

Scheme II shows our procedures for the conversion of isoxazolidine 16 to 9α -anilino-PGF (+)-27. The key step involved an asymmetric reduction of the enone group in 24 with (S)-BI-NAL-H,^{7,8} which gave diastereomeric allylic alcohols (+)-27 (39% yield, 86% e.e.) and (-)-29 (38% yield, 88% e.e.) in 80% overall yield. Reductive cleavage¹³⁻¹⁵ of the N-O bond in (+)-27 afforded an 88% yield of 9α -anilino-PGF (+)-33 ([α]²⁵_D +32.2° (c 0.43, THF)). Finally, we cyclized alkyne (+)-33 with PdCl₂(MeCN)₂ and LiCl17 to give a 70% yield of the desired 6.9α -anilino-PGI₂ $(+)-34 ([\alpha]^{25} + 12.7^{\circ} (c 0.13, THF)).$

In conclusion, $11\alpha,9\alpha$ -epoxyimino-PGH₁ and -PGH₂ were synthesized efficiently by a novel intramolecular nitrone-alkene cycloaddition. These compounds were degraded by oxidative ring-opening, by reductive ring-cleavage, or by reductive cyclization to give (-)-PGE₁ and prostanoids in the PGF₁, PGF₂, and PGI₂ series. The newly developed biomimetic, cascade-type strategy was proven versatile for the synthesis of various types of prostanoids.

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Total Synthesis of Sialyl Dimeric Lex

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Recent discoveries identifying sialyl Lex-type molecules as the binding ligands of endothelial leukocyte adhesion molecule-1 (ELAM-1) generated considerable excitement in chemical, biological, and medical circles.¹⁻⁶ Given the connection of ELAM-1 to leukocytes and its role in their recruitment to inflammation sites, ELAM-1 binding molecules are emerging as important biological tools and potential agents to treat inflammation and related disorders. Among the naturally occurring ELAM-1

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