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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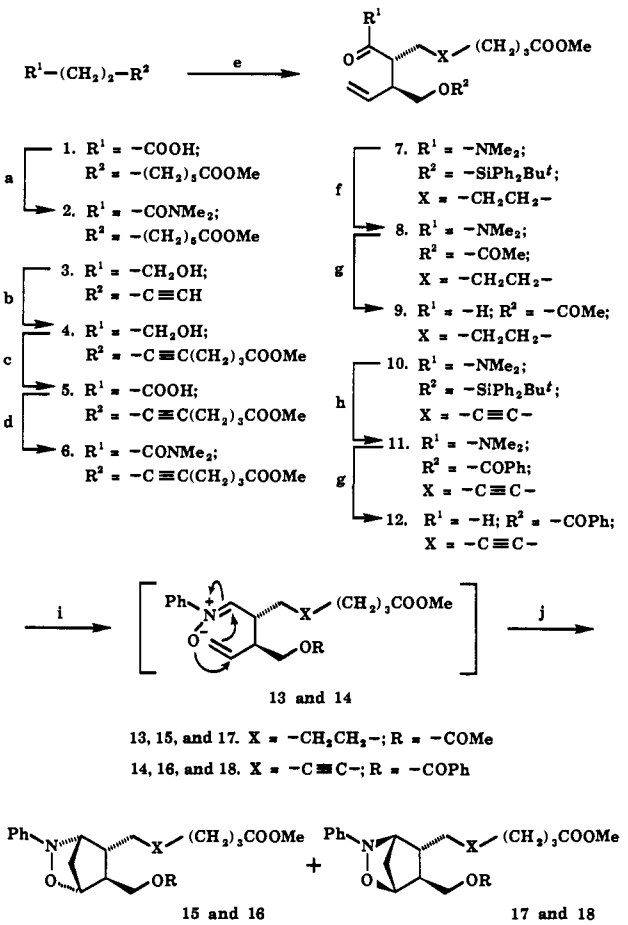
Prostaglandins (PGs) exist in most mammalian tissues.[1] Isolation of PGs from natural biosynthetic sources cannot meet their medicinal demand.[2] Total synthesis thus remains the only means by which sufficient quantities of prostanoids can be made available.[2,3] Herein we report a novel biomimetic, cascade-type synthesis[4] 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** → **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

Scheme I[a]



[a] a: (1) $SOCl_2$, 80 °C; (2) Me_2NH, H_2O (87%). b: (1) $LiNH_2$, NH_3, Et_2O; (2) $Br(CH_2)_3C(OMe)_3$, −33 °C (84%).[18,19] c: CrO_3, 4.0 M H_2SO_4 (aq), Me_2CO, room temperature (83%). d: $(COCl)_2$, Me_2NH, room temperature (87%). e: (1) MeOTf, CH_2Cl_2, room temperature; (2) *cis*-$LiOCH_2CH{=}CHCH_2OSiPh_2Bu^t$, THF, Δ (for **2** → **7**, 69%; for **6** → **10**, 72%).[5] f: (1) *n*-Bu_4NF, THF; (2) Ac_2O, Et_3N, room temperature (98%). g: (1) MeOTf, CH_2Cl_2, room temperature; (2) L-Selectride, THF, −78 °C; (3) H_3O^+ (for **8** → **9**, 50% for **11** → **12**, 64%).[6] h: (1) *n*-Bu_4NF, THF; (2) $(PhCO)_2O$, Et_3N, room temperature (98%). i: PhNHOH, 5A molecular sieves, solvent. j: Δ.[4]

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 (−)-11α,9α-epoxyimino-PGH_1 sodium salt **26** in 88% yield.

An efficient method for the conversion of epoxyimino-PGH (−)-**25** to (−)-PGE_1 is appealing because PGEs possess therapeutic value[9] 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 (−)-PGE_1 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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§ Cordially dedicated to Professor James P. Collman on the occasion of his 60th birthday.

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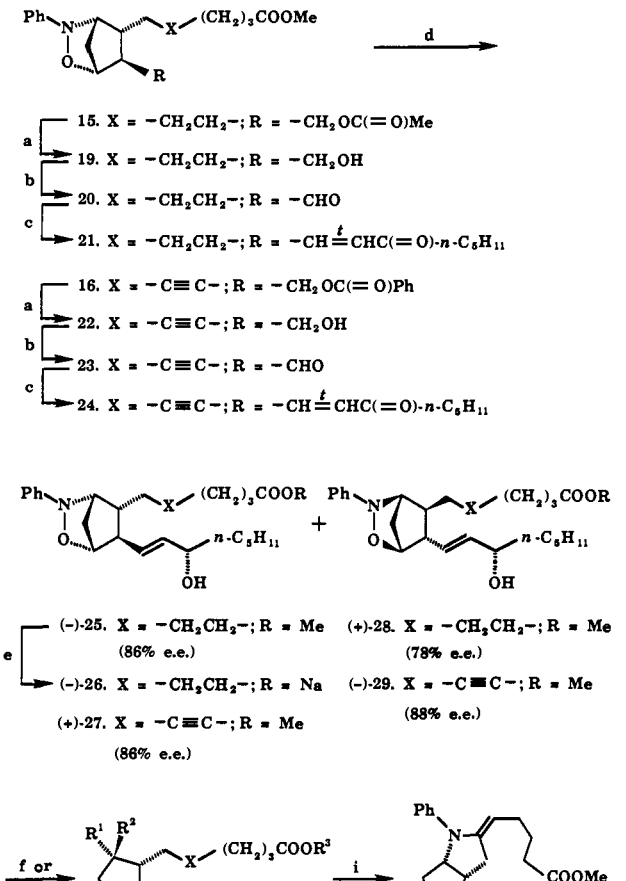
Scheme II[a]



[a] a: KOH, MeOH (for **15** → **19**, 82%; for **16** → **22**, 88%). b: DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −60 °C (for **19** → **20**, 93%; for **22** → **23**, 92%). c: $(MeO)_2P(=O)CHNaC(=O)$-*n*-C_5H_{11}, DME, 0 °C (for **20** → **21**, 92%; for **23** → **24**, 88%).[20] d: (*S*)-BINAL-H, THF, −100 to −78 °C[7,8] (for **21** → (−)-**25** (36%) + (+)-**28** (38%); for **24** → (+)-**27** (39%) + (−)-**29** (41%)). e: NaOH, H_2O, MeOH (88%). f: (1) *m*-CPBA, CH_2Cl_2, 0 °C; (2) NH_4Cl, H_2O (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: $PdCl_2(MeCN)_2$, LiCl, MeCN (70%).[17]

cleavage of the N–O bond in (−)-**25** with Zn dust and glacial acetic acid[13-15] gave an 89% yield of 9α-anilino-PGF_1 (+)-**32** ($[\alpha]^{25}_D$ +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 calculation[16] indicated that the PGI_2 enamine analogue was ~0.81 kcal/mol more stable than the parent enol ether toward hydrolysis.

We planned to synthesize a 6,9α-anilino-PGI_2 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*)-BINAL-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 cleavage[13-15] of the N–O bond in (+)-**27** afforded an 88% yield of 9α-anilino-PGF (+)-**33** ($[\alpha]^{25}_D$ +32.2° (*c* 0.43, THF)). Finally, we cyclized alkyne (+)-**33** with $PdCl_2(MeCN)_2$ and LiCl[17] to give a 70% yield of the desired 6,9α-anilino-PGI_2 (+)-**34** ($[\alpha]^{25}_D$ +12.7° (*c* 0.13, THF)).

In conclusion, 11α,9α-epoxyimino-PGH_1 and -PGH_2 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 (−)-PGE_1 and prostanoids in the PGF_1, PGF_2, and PGI_2 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 Le^x

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Recent discoveries identifying sialyl Le^x-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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