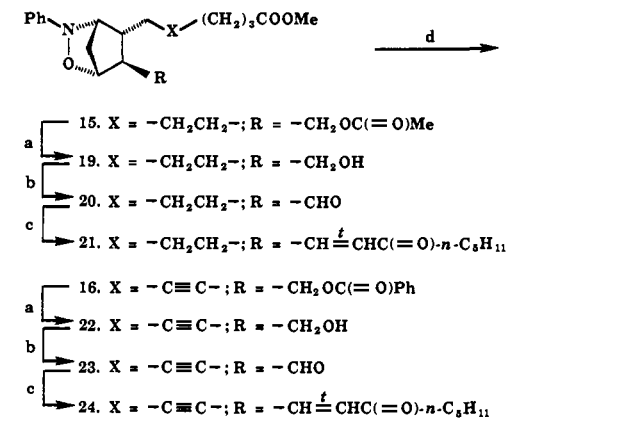
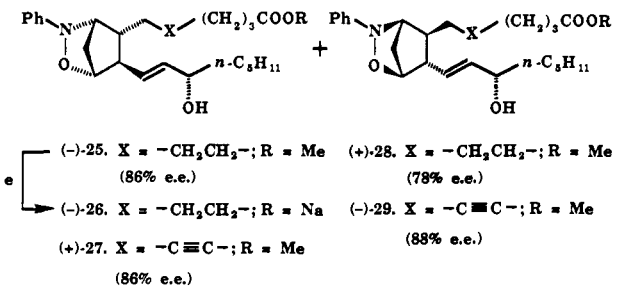
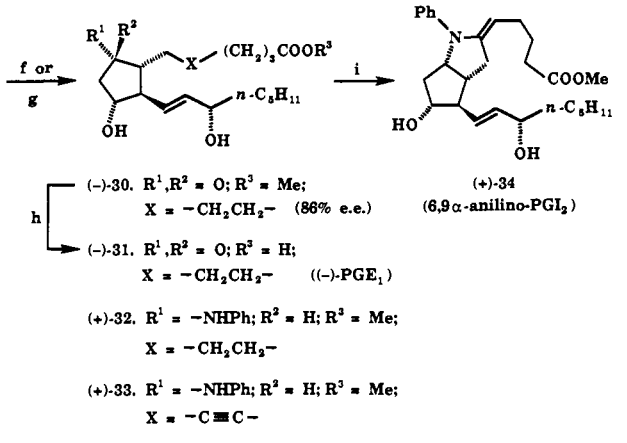
Scheme II[a]







[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.

Acknowledgment. For financial support, we are indebted to the National Institutes of Health for Biomedical Research Support Grant S07 RR7041; to the National Science Council of the Republic of China (NSC 81-0208-M007-59); and to Academia Sinica. B. A. Gilbert thanks Dr. Henry Sonneborn III for a fellowship.

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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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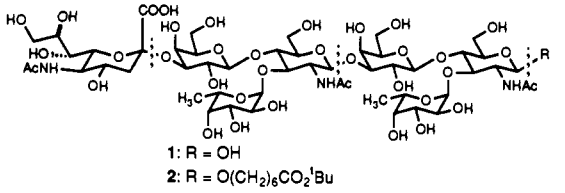
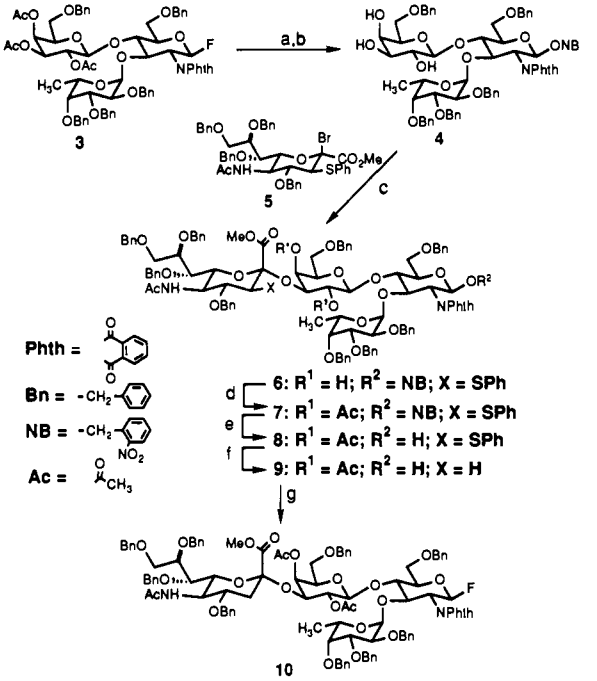
Scheme I[a]



[a]Structures of natural sialyl di-Le^x (**1**) and derivative **2**.

Scheme II[a]

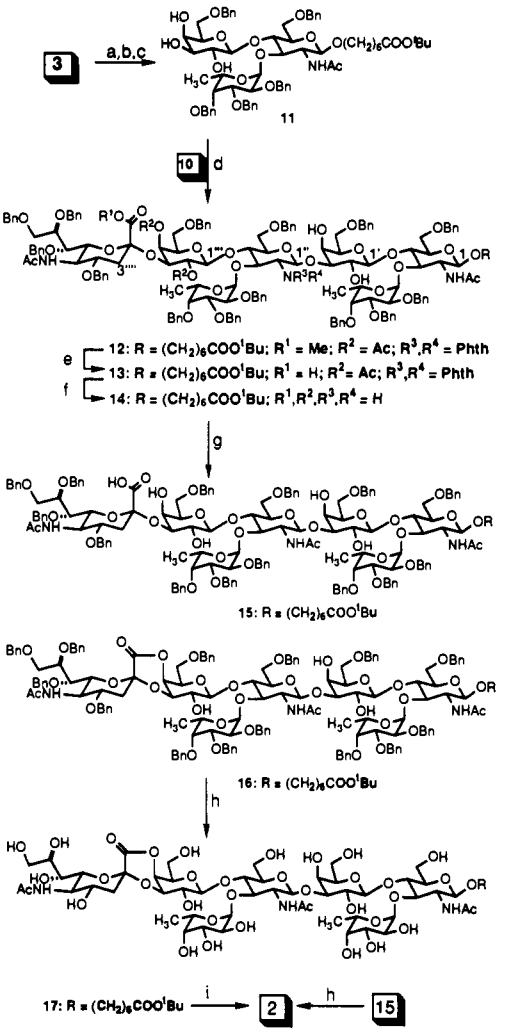


[a]Synthesis of functionalized monomeric sialyl Le^x (**10**). Reagents and conditions: (a) 3.5 equiv of AgOTf, 3.5 equiv of $HfCp_2Cl_2$, 2.5 equiv of *o*-nitrobenzyl alcohol, 4-Å molecular sieves, CH_2Cl_2, -40 to 5 °C, 3 h, 94%; (b) NaOMe (cat.), MeOH, 25 °C, 3 h, 98%; (c) 3.0 equiv of $Hg(CN)_2$, 1.0 equiv of $HgBr_2$, 1.8 equiv of **4**, 4-Å molecular sieves, CCl_4, 0 to 25 °C, 3 h, 56% based on consumed **4**; (d) Ac_2O (xs), pyridine (xs), DMAP (cat.), CH_2Cl_2, 0 to 25 °C, 48 h, 86%; (e) THF-H_2O (10:1), *hν*, 0 °C, 1.0 h, 82% (plus 10% recovered starting material); (f) 10 equiv of Ph_3SnH, 0.9 equiv of AIBN, toluene, 130 °C, 8 h, 42% (plus 45% recovered starting material); (g) 2.0 equiv of DAST, CH_2Cl_2, -78 °C, 15 min, 78%.

binding oligosaccharides, sialyl dimeric Le^x (S-diLe^x (**1**), Scheme I) occupies a prominent position due to its molecular complexity and potential as a highly potent substrate. Furthermore, S-diLe^x (**1**) is identified as a tumor-associated oligosaccharide and, thus, it may serve as a marker for tumor cell targeting.[7-10] Herein, we report the first total synthesis of this molecule, equipped with an anchoring device (compound **2**) for further chemical and biological explorations.

The present synthesis relies on a number of previous developments reported from these laboratories: (a) the utilization of the phenylthio group as an auxiliary to facilitate and stereochemically control the formation of either α- or β-2-deoxyglycosides[11,12] and

Scheme III[a]



[a]Synthesis of sialyl di-Le^x compound (**2**). Reagents and conditions: (a) 4.0 equiv of AgOTf, 4.0 equiv of $HfCp_2Cl_2$, 2.5 equiv of HO-$(CH_2)_6COO^tBu$, 4-Å molecular sieves, CH_2Cl_2, -40 to -10 °C, 2 h, 87%; (b) 30 equiv of hydrazine hydrate, MeOH-benzene (1:1), 80 °C, 6 h; (c) Ac_2O (xs), MeOH-CH_2Cl_2 (1:1), 0 °C, 4 h, 83% over two steps; (d) 4.5 equiv of AgOTf, 5.0 equiv of $HfCp_2Cl_2$, 2.5 equiv of **11**, 4-Å molecular sieves, CH_2Cl_2, -20 to 25 °C, 18 h, 51% based on consumed **11**; (e) 6 equiv of LiI, pyridine, 120 °C, 3 h, 80% (plus 17% recovered starting material); (f) 50 equiv of hydrazine hydrate, MeOH-benzene (1:1), 80 °C, 8 h; (g) Ac_2O (xs), MeOH-CH_2Cl_2 (1:1), 0 °C, 1 h, 75% mixture of acid and lactone over two steps; (h) H_2, $Pd(OH)_2$ (cat.), MeOH, 25 °C, 48 h, 95%; (i) H_2O, 2 h, 25 °C, 100%.

(b) the established procedure for the synthesis of the simpler, monomeric sialyl Le^x.[13] For the synthetic strategy of this target, we envisioned stereocontrolled construction of the three indicated glycoside bonds (see dotted lines, Scheme I) to assemble the requisite skeleton rapidly and convergently, followed by deprotection to deliver **2**.

Scheme II summarizes the construction of advanced key intermediate **10** from building blocks **3** and **5**. The Le^x-derivative **3**[14] was synthesized by modifications of chemistry developed in these laboratories[13] (see the supplementary material) and was converted to the trihydroxy compound **4** by glycosylation (94% yield) followed by deacetylation (98% yield). The sialic acid derivative **5** was synthesized by a modification of Ogawa's[12]

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(14) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

method (see the supplementary material) and was coupled to **4** under the influence of $Hg(CN)_2$–$HgBr_2$ to regio- and stereospecifically afford tetrasaccharide **6** in 56% yield.[15-17] This remarkable difference in the reactivities of the three hydroxyl groups in **4** is noteworthy since it allows rapid oligosaccharide construction without protecting groups (vide infra for a second application of this finding).[18] Acetylation of the remaining hydroxyl groups in **6** led to **7** (86%); subsequent photolytic cleavage of the *o*-nitrobenzyl ether led to lactol **8** (82%). Removal of the phenylthio group by Ph_3SnH–AIBN-initiated radical chemistry required heating to 130 °C and recycling, furnishing compound **9** (42% yield, plus 45% starting material for each cycle). Finally, treatment of **9** with DAST resulted in formation of the requisite fluoride **10** in 78% yield (ca. 4:1 ratio of β- and α-anomers).

Scheme III exhibits the continuation of the buildup toward S-diLe^x compound **2**. Thus, trisaccharide **3** was first converted to trihydroxyglycoside **11** by glycosylation (87% yield) followed by concomitant deacetylation–dephthaloylation using hydrazine and finally selective N-acetylation (83% over two steps). Again, by taking advantage of the reactivity differences between the three hydroxyl groups in **11**, the next glycosylation step (using the tetrasaccharide donor **10**) was successfully carried out without protection, leading to sialylated compound **12**[17] in 51% yield.[19] Generation of the carboxylic acid **13** from its methyl ester was best accomplished with lithium iodide in pyridine (120 °C, 80%, plus 17% recovered starting material); subsequent exposure to hydrazine at 80 °C removed both the phthalimido and the acetate groups, resulting in the formation of the amino acid **14**. Acetylation of **14** with excess acetic anhydride in methanol–methylene chloride furnished a mixture of polyhydroxy acid **15** and its δ-lactone **16** (ca. 1:1 ratio, 75% overall yield from **13**). Finally, debenzylation of **15** by hydrogenolysis proceeded smoothly to produce the targeted compound **2** in 95% yield. Lactone **17** was also debenzylated by catalytic hydrogenolysis to afford the corresponding polyhydroxylated lactone (95% yield), which was found to open up quantitatively to the target oligosaccharide **2** on standing in D_2O (NMR tube, 2 h, 25 °C).

The described chemistry renders S-diLe^x and its derivatives such as **2** readily available in pure form for extensive biological investigations. Further studies envisioned in this field may expand the library of biological tools and provide therapeutic agents in the area of inflammation and related conditions.

Acknowledgment. We express our many thanks to Drs. Dee Huang and Gary Siuzdak of The Scripps Research Institute for their excellent NMR and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health and The Scripps Research Institute.

Supplementary Material Available: Schemes for the synthesis of compounds **3** and **5** and listings of selected physical data for compounds **4**, **6**, **9**, **11**, **12**, **16**, and **2** (11 pages). Ordering information is given on any current masthead page.

(15) For similar couplings, see: Okamoto, K.; Goto, T. *Tetrahedron* **1990**, *46*, 5835.

(16) The stereochemistry of the newly generated glycoside bond in **6** was tentatively assigned on mechanistic considerations and was confirmed by the observation of a doublet in the gated proton-decoupled ^{13}C NMR spectrum of **9** (125 MHz, $CDCl_3$, δ 168.5, $J_{C\text{-}1S.A.,H\text{-}3axS.A.}$ = 5.5 Hz); see: Hori, H.; Nakajimia, T.; Nishida, Y.; Ohru, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317.

(17) The regiochemistry of the coupling reaction to give **6** was proven by ^1H NMR analysis of the corresponding bis(acetate) **7**, which exhibited the expected large downfield chemical shifts for the galactose C-2 and C-4 protons [(500 MHz, $CDCl_3$) **6**: C-2, δ 3.36; C-4, 4.04. **7**: C-2, δ 5.07; C-4, 5.46]; similar observations were made for **12**. The bis(acetate) of **12** exhibited two new downfield peaks in the ^1H NMR spectrum corresponding to the newly acetylated 2 and 4 positions of galactose [(500 MHz, benzene-d_6) bis(acetate) of **12**: C-2′, δ 5.19; C-4′, 5.68]. The pre-existing acetylated C-2‴ and C-4‴ positions exhibited similar downfield chemical shifts [(500 MHz, benzene-d_6) **12**: C-2‴, δ 5.47; C-4‴ δ 5.81. bis(acetate) of **12**: C-2‴ δ 5.49; C-4‴ δ 5.80].

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(19) From the two anomeric fluorides of **10**, only the β-anomer reacted, the α-anomer being recovered unchanged. The yield of 51% was based on consumed triol **11**.

Direct Observation of the Formation and Rearrangement of Carbene/Allyl Sulfide Ylides

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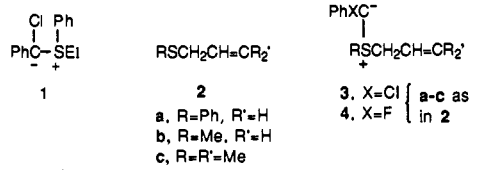
More than 25 years ago, Parham and Groen reported that dichlorocarbene reacted with acyclic allylic sulfides to form sulfonium ylides that subsequently underwent "allylic rearrangement" (Scheme I).[1] In current terminology, the ylide would be said to undergo a [2,3] sigmatropic rearrangement.[2] Now, we have used laser flash photolysis (LFP) to probe the closely related reactions of phenylchlorocarbene (PhCCl) and phenylfluorocarbene (PhCF) with phenyl allyl sulfide, methyl allyl sulfide, and γ,γ-dimethylallyl methyl sulfide. We describe here the first direct observational and absolute kinetic studies of both the formation and rearrangement of the intermediate carbene/allyl sulfide ylides.

LFP-generated carbenes react with thiophene and thioanisole to give spectroscopically observable *S*-ylides.[3] Similarly, we find that LFP[4] of phenylchlorodiazirine[5] in PhSEt–pentane affords absorptions at 280–340 and 380–450 nm, λ_{max} 310 and 420 nm. These absorptions are stable for >10 μs, are not observed in the absence of sulfide,[6,7] and are attributed to ylide **1**. Appropriately, the appearance of **1**, monitored at 420 nm, is first-order in [sulfide], with $k_f = (2.9 \pm 0.2) \times 10^9$ M^{-1} s^{-1}.

LFP of phenylchloro- and phenylfluorodiazirine[8] gave PhCCl[7] and PhCF,[9] respectively, which were readily captured by allylic sulfides **2a–c** in pentane or isooctane solutions to afford the transient ylides **3a–c** (from PhCCl) and **4a–c** (from PhCF). The ylides exhibited absorptions analogous to those of **1** but, in contrast to **1**, ylides **3** and **4** were unstable. Their decay made it difficult to directly assess k_f for their formation, but this could be accomplished using the pyridine probe method.[3]



Thus, LFP-generated PhCCl reacted with 8×10^{-4} M pyridine in pentane to afford the known pyridinium ylide.[3] The first-order rate constant for the appearance of this ylide (monitored at 480 nm, where the *S*-ylides do not absorb), plotted against (e.g.) the concentration of (1–9) $\times 10^{-4}$ M added sulfide **2a**, gave a linear correlation whose slope (2.3×10^9 M^{-1} s^{-1}) was taken as k_f for the formation of *S*-ylide **3a**.[10] Rate constants for the formation of *S*-ylides **3** and **4** from reactions of PhCCl and PhCF with

(1) (a) Parham, W. E.; Groen, S. H. *J. Org. Chem.* **1964**, *29*, 2214. (b) Parham, W. E.; Groen, S. H. *Ibid.* **1965**, *30*, 728. (c) Parham, W. E.; Groen, S. H. *Ibid.* **1966**, *31*, 1694.

(2) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; pp 956 f.

(3) Jackson, J. E.; Soundararajan, N.; Platz, M. S.; Liu, M. T. H. *J. Am. Chem. Soc.* **1988**, *110*, 5595.

(4) The LFP conditions were 351 nm, 50–80 mJ, 14 ns. For a description of our apparatus, see: Moss, R. A.; Shen, S.; Hadel, L. M.; Kmiecik-Lawrynowicz, G.; Wlostowska, J.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1987**, *109*, 4341.

(5) Graham, W. H. *J. Am. Chem. Soc.* **1965**, *87*, 4396.

(6) PhCCl also has λ_{max} 310 nm (isooctane), but it decays on the microsecond time scale.[7] The reaction of PhCF with PhSEt is analogous to that of PhCCl.

(7) Turro, N. J.; Butcher, J. A., Jr.; Moss, R. A.; Guo, W.; Munjal, R. C.; Fedorynski, M. *J. Am. Chem. Soc.* **1980**, *102*, 7576.

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(9) Cox, D. P.; Gould, I. R.; Hacker, N. P.; Moss, R. A.; Turro, N. J. *Tetrahedron Lett.* **1983**, *24*, 5313.

(10) This value is similar to $k_f = 2.9 \times 10^9$ M^{-1} s^{-1} for the formation of **1** from PhCCl and PhSEt; see above.

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