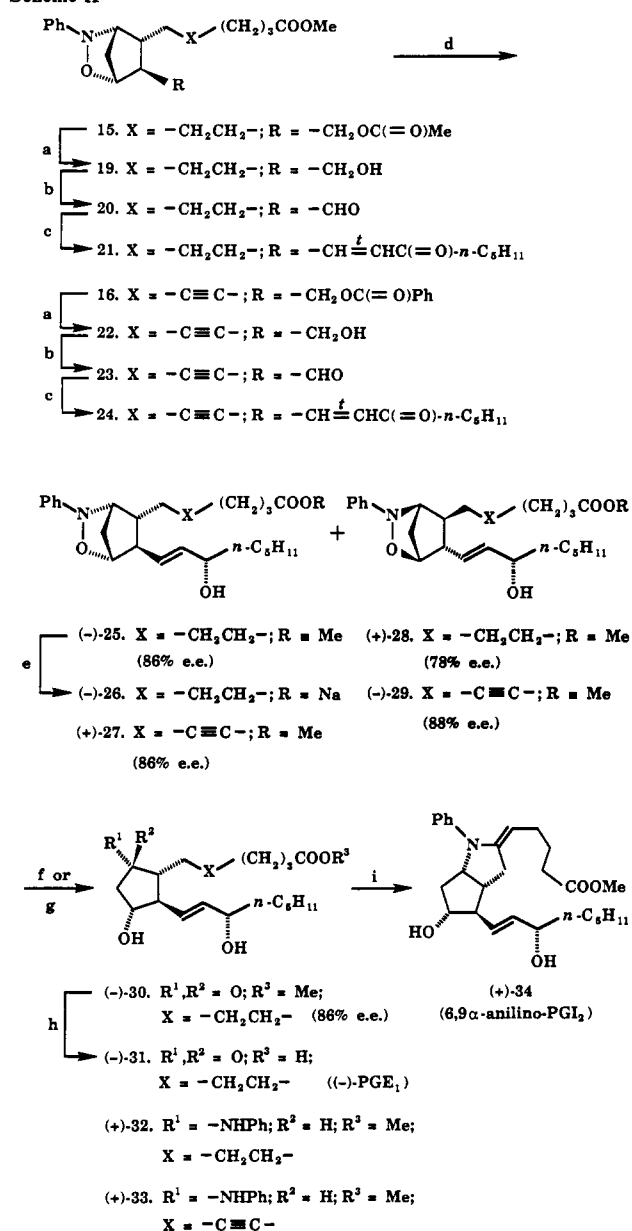


Scheme II<sup>a</sup>

<sup>a</sup>a: KOH, MeOH (for 15 → 19, 82%; for 16 → 22, 88%). b: DMSO, (COCl)<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, -60 °C (for 19 → 20, 93%; for 22 → 23, 92%). c: (MeO)<sub>2</sub>P(=O)CHNAC(=O)-n-C<sub>8</sub>H<sub>11</sub>, DME, 0 °C (for 20 → 21, 92%; for 23 → 24, 88%).<sup>20</sup> d: (S)-BINAL-H, THF, -100 to -78 °C;<sup>7,8</sup> (for 21 → (-)-25 (36%) + (+)-28 (38%); for 24 → (+)-27 (39%) + (-)-29 (41%)). e: NaOH, H<sub>2</sub>O, MeOH (88%). f: (1) m-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (2) NH<sub>4</sub>Cl, H<sub>2</sub>O (for (-)-25 → (-)-30, 65%).<sup>10,11</sup> g: Zn, HOAc, 55 °C (for (-)-25 → (+)-32, 89%; for (+)-27 → (+)-33, 88%).<sup>13-15</sup> h: Bakers' yeast, 0.1 M phosphate buffer, pH 7.0 (72%).<sup>21</sup> i: PdCl<sub>2</sub>(MeCN)<sub>2</sub>, LiCl, MeCN (70%).<sup>17</sup>

cleavage of the N-O bond in (-)-25 with Zn dust and glacial acetic acid<sup>13-15</sup> gave an 89% yield of 9α-anilino-PGF<sub>1</sub> (+)-32 ([α]<sub>D</sub><sup>25</sup> +25.8° (c 0.37, THF)).

Prostacyclin (i.e., PGI) and its analogues are difficult synthetic targets but have great medicinal potential.<sup>9</sup> Results from our AM1 calculation<sup>16</sup> indicated that the PGI<sub>2</sub> 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<sub>2</sub> via an epoxy-imino-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 nitron 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,<sup>7,8</sup> which gave diastereomeric allylic alcohols (+)-27 (39% yield, 86% e.e.) and (-)-29 (38% yield, 88% e.e.) in 80% overall yield. Reductive cleavage<sup>13-15</sup> of the N-O bond in (+)-27 afforded an 88% yield of 9α-anilino-PGF (+)-33 ([α]<sub>D</sub><sup>25</sup> +32.2° (c 0.43, THF)). Finally, we cyclized alkyne (+)-33 with PdCl<sub>2</sub>(MeCN)<sub>2</sub> and LiCl<sup>17</sup> to give a 70% yield of the desired 6,9α-anilino-PGI<sub>2</sub> (+)-34 ([α]<sub>D</sub><sup>25</sup> +12.7° (c 0.13, THF)).

In conclusion, 11α,9α-epoxyimino-PGH<sub>1</sub> and -PGH<sub>2</sub> were synthesized efficiently by a novel intramolecular nitron-alkene cycloaddition. These compounds were degraded by oxidative ring-opening, by reductive ring-cleavage, or by reductive cyclization to give (-)-PGE<sub>1</sub> and prostanooids in the PGF<sub>1</sub>, PGF<sub>2</sub>, and PGI<sub>2</sub> series. The newly developed biomimetic, cascade-type strategy was proven versatile for the synthesis of various types of prostanooids.

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## Total Synthesis of Sialyl Dimeric Le<sup>x</sup>

K. C. Nicolaou,\* C. W. Hummel, and Y. Iwabuchi

Department of Chemistry, The Scripps Research  
Institute, 10666 North Torrey Pines Road  
La Jolla, California 92037

Department of Chemistry  
University of California at San Diego  
La Jolla, California 92093

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Recent discoveries identifying sialyl Le<sup>x</sup>-type molecules as the binding ligands of endothelial leukocyte adhesion molecule-1 (ELAM-1) generated considerable excitement in chemical, biological, and medical circles.<sup>1-6</sup> 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

\* Author to whom correspondence should be addressed at The Scripps Research Institute.

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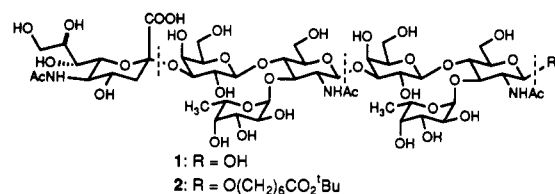
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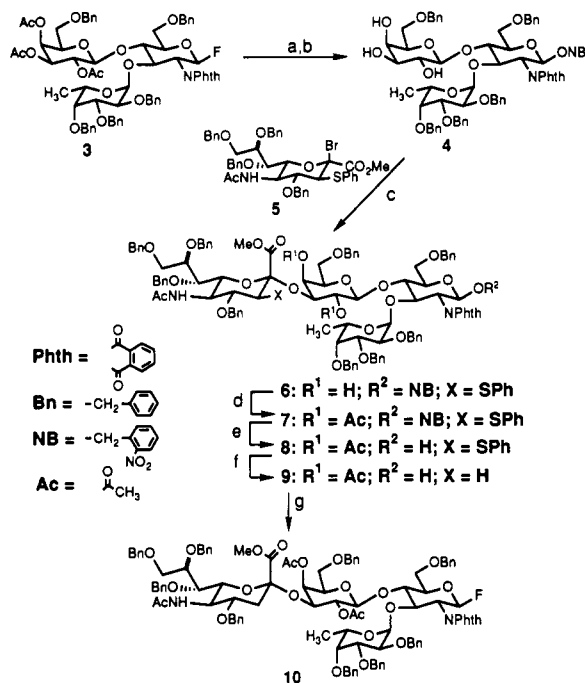
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Scheme I<sup>a</sup>

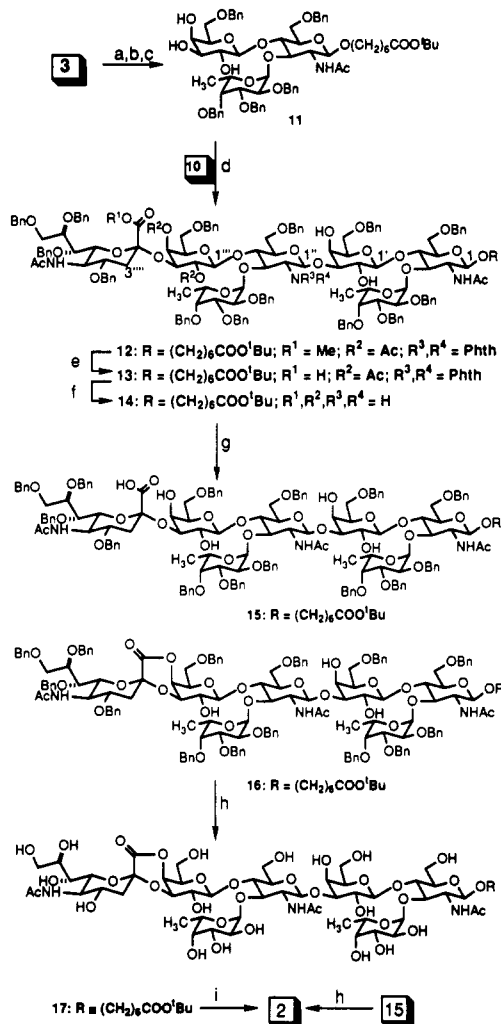
<sup>a</sup> Structures of natural sialyl di-Le<sup>x</sup> (1) and derivative 2.

Scheme II<sup>a</sup>

<sup>a</sup> Synthesis of functionalized monomeric sialyl Le<sup>x</sup> (10). Reagents and conditions: (a) 3.5 equiv of AgOTf, 3.5 equiv of HfCp<sub>2</sub>Cl<sub>2</sub>, 2.5 equiv of *o*-nitrobenzyl alcohol, 4-Å molecular sieves, CH<sub>2</sub>Cl<sub>2</sub>, -40 to 5 °C, 3 h, 94%; (b) NaOMe (cat.), MeOH, 25 °C, 3 h, 98%; (c) 3.0 equiv of Hg(CN)<sub>2</sub>, 1.0 equiv of HgBr<sub>2</sub>, 1.8 equiv of 4, 4-Å molecular sieves, CCl<sub>4</sub>, 0 to 25 °C, 3 h, 56% based on consumed 4; (d) Ac<sub>2</sub>O (xs), pyridine (xs), DMAP (cat.), CH<sub>2</sub>Cl<sub>2</sub>, 0 to 25 °C, 48 h, 86%; (e) THF-H<sub>2</sub>O (10:1), *hν*, 0 °C, 1.0 h, 82% (plus 10% recovered starting material); (f) 10 equiv of Ph<sub>3</sub>SnH, 0.9 equiv of AIBN, toluene, 130 °C, 8 h, 42% (plus 45% recovered starting material); (g) 2.0 equiv of DAST, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 15 min, 78%.

binding oligosaccharides, sialyl dimeric Le<sup>x</sup> (S-diLe<sup>x</sup> (1), Scheme I) occupies a prominent position due to its molecular complexity and potential as a highly potent substrate. Furthermore, S-diLe<sup>x</sup> (1) is identified as a tumor-associated oligosaccharide and, thus, it may serve as a marker for tumor cell targeting.<sup>7-10</sup> 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<sup>11,12</sup> and

Scheme III<sup>a</sup>

<sup>a</sup> Synthesis of sialyl di-Le<sup>x</sup> compound (2). Reagents and conditions: (a) 4.0 equiv of AgOTf, 4.0 equiv of HfCp<sub>2</sub>Cl<sub>2</sub>, 2.5 equiv of HO-(CH<sub>2</sub>)<sub>6</sub>COO<sup>t</sup>Bu, 4-Å molecular sieves, CH<sub>2</sub>Cl<sub>2</sub>, -40 to -10 °C, 2 h, 87%; (b) 30 equiv of hydrazine hydrate, MeOH-benzene (1:1), 80 °C, 6 h; (c) Ac<sub>2</sub>O (xs), MeOH-CH<sub>2</sub>Cl<sub>2</sub> (1:1), 0 °C, 4 h, 83% over two steps; (d) 4.5 equiv of AgOTf, 5.0 equiv of HfCp<sub>2</sub>Cl<sub>2</sub>, 2.5 equiv of 11, 4-Å molecular sieves, CH<sub>2</sub>Cl<sub>2</sub>, -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<sub>2</sub>O (xs), MeOH-CH<sub>2</sub>Cl<sub>2</sub> (1:1), 0 °C, 1 h, 75% mixture of acid and lactone over two steps; (h) H<sub>2</sub>, Pd(OH)<sub>2</sub> (cat.), MeOH, 25 °C, 48 h, 95%; (i) H<sub>2</sub>O, 2 h, 25 °C, 100%.

(b) the established procedure for the synthesis of the simpler, monomeric sialyl Le<sup>x</sup>.<sup>13</sup> 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<sup>x</sup>-derivative 3<sup>14</sup> was synthesized by modifications of chemistry developed in these laboratories<sup>13</sup> (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<sup>12</sup>

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method (see the supplementary material) and was coupled to **4** under the influence of  $\text{Hg}(\text{CN})_2\text{-HgBr}_2$  to regio- and stereospecifically afford tetrasaccharide **6** in 56% yield.<sup>15-17</sup> 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).<sup>18</sup> 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  $\text{Ph}_3\text{SnH-AIBN}$ -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  $\beta$ - and  $\alpha$ -anomers).

Scheme III exhibits the continuation of the buildup toward S-diLe<sup>x</sup> 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**<sup>17</sup> in 51% yield.<sup>19</sup> 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  $\delta$ -lactone **16** (ca. 1:1 ratio, 75% overall yield from **13**). Finally, debenzoylation of **15** by hydrogenolysis proceeded smoothly to produce the targeted compound **2** in 95% yield. Lactone **17** was also debenzoylated 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  $\text{D}_2\text{O}$  (NMR tube, 2 h, 25 °C).

The described chemistry renders S-diLe<sup>x</sup> 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.

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**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.

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(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  $^{13}\text{C}$  NMR spectrum of **9** (125 MHz,  $\text{CDCl}_3$ ,  $\delta$  168.5,  $J_{\text{C-1S,A,H-3aaS,A}} = 5.5$  Hz); see: Hori, H.; Nakajima, T.; Nishida, Y.; Ohru, H.; Meguro, H. *Tetrahedron Lett.* **1988**, *29*, 6317.

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(19) From the two anomeric fluorides of **10**, only the  $\beta$ -anomer reacted, the  $\alpha$ -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

Robert A. Moss,\* Guo-Jie Ho, and Claudia Sierakowski

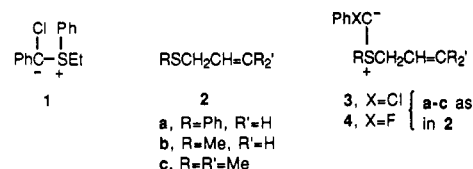
Department of Chemistry, Rutgers  
The State University of New Jersey  
New Brunswick, New Jersey 08903

Received December 27, 1991

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).<sup>1</sup> In current terminology, the ylide would be said to undergo a [2,3] sigmatropic rearrangement.<sup>2</sup> 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  $\gamma,\gamma$ -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.<sup>3</sup> Similarly, we find that LFP<sup>4</sup> of phenylchlorodiazirine<sup>5</sup> in PhSEt-pentane affords absorptions at 280-340 and 380-450 nm,  $\lambda_{\text{max}}$  310 and 420 nm. These absorptions are stable for  $>10$   $\mu\text{s}$ , are not observed in the absence of sulfide,<sup>6,7</sup> and are attributed to ylide **1**. Appropriately, the appearance of **1**, monitored at 420 nm, is first-order in [sulfide], with  $k_f = (2.9 \pm 0.2) \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ .

LFP of phenylchloro- and phenylfluorodiazirine<sup>8</sup> gave PhCCl<sup>7</sup> and PhCF,<sup>9</sup> 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.<sup>3</sup>



Thus, LFP-generated PhCCl reacted with  $8 \times 10^{-4} \text{ M}$  pyridine in pentane to afford the known pyridinium ylide.<sup>3</sup> 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  $(1-9) \times 10^{-4} \text{ M}$  added sulfide **2a**, gave a linear correlation whose slope ( $2.3 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ ) was taken as  $k_f$  for the formation of S-ylide **3a**.<sup>10</sup> Rate constants for the formation of S-ylides **3** and **4** from reactions of PhCCl and PhCF with

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(6) PhCCl also has  $\lambda_{\text{max}}$  310 nm (isooctane), but it decays on the microsecond time scale.<sup>7</sup> The reaction of PhCF with PhSEt is analogous to that of PhCCl.

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