

## A Straightforward Synthesis of K-7174, a GATA-Specific Inhibitor

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K-7174, a GATA-specific inhibitor, is a putative anti-inflammatory agent that attenuates effects of inflammatory cytokines in certain cell types. An expeditious four-step synthesis of K-7174 is described in this paper. The route employs Wittig olefination and bis-alkylation of homopiperazine as the key reactions. The iodine-catalyzed isomerization of the *Z*-isomer results in complete conversion to the *E*-isomer is the highlight of our synthetic endeavors.

**Key Words :** K-7174, Wittig reaction, GATA-inhibitor, Iodine-catalyzed isomerization

### Introduction

Piperazine and homopiperazine skeleton are considered as privileged templates in drug discovery.<sup>1</sup> These core structures are found in numerous biologically active compounds and drugs for a number of indication and mechanisms. In recent years, a variety of 1,4-diazepines have been regarded as peptidomimetic scaffolds with a conformationally constrained core,<sup>2a</sup> anti-HIV agents,<sup>2b</sup> and inhibitors of protein kinase, caspase, and matrix metalloproteinase.<sup>2c</sup> More particularly, the pharmaceutical use of *N,N'*-bis[5-(3,4,5-trimethoxyphenyl)-4-pentenyl]homopiperazine-dihydrochloride (**1**, K-7174) containing homopiperazine motif as a core unit was described as an insulin secretagogues, hypoglycemics, and antidiabetic drugs.<sup>3</sup>

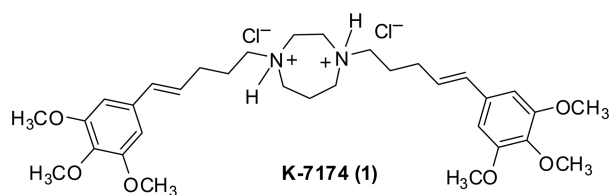
Moreover, K-7174 (**1**) (Figure 1) is also able to elicit various obesity-related inflammations. The obesity-related inflammation is emerging as a major root of cardiovascular diseases and type 2 diabetes, is caused by an expansion of white adipose tissue upon alteration of energy balance.<sup>4</sup> It has been observed that adipocyte precursors and immunocompetent cells like macrophages share similar functions.<sup>5</sup> GATA-2 transcription factor is an inhibitor of adipogenesis and an activator of vascular cells and hence consider to be a new target in prevention and treatment of obesity-related inflammations.<sup>6</sup> Furthermore, K-7174 a cell adhesive inhibitor, acting through the regulation of GATA is useful into the development of new therapeutics for atherosclerosis and other inflammation based disorders.<sup>7,8</sup> Umetani *et al.* reported that K-7174 inhibited cell adhesion by regulating the binding activity to GATA motifs in vascular cell adhesion

molecule-1 (VCAM-1) gene promoter specifically.<sup>7</sup> Also analysis of preendothelin-1 promoter indicated that K-7174 blocks not only binding activity to VCAM-1 promoter GATA motifs, but also binding to GATA motifs in endothelial genes. Imagawa *et al.* have investigated the potential of K-7174, to improve erythropoietin (Epo) production after inhibition by IL-1 $\alpha$ , TNF- $\beta$ , or L-NMMA treatment in Hep3B cell and hence, raise the possibility of using K-7174 as a novel drug for treatment of anemia of chronic diseases (ACD) and for anemia associated with renal diseases.<sup>9</sup> Anemia commonly occurs in patients with chronic diseases such as malignancies, chronic inflammatory states, or infections. One common pathogenesis of anemia of ACD and with renal disease appears to be stimulation of GATA binding activity by interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), or NG-monomethyl L-arginine (L-NMMA), which inhibits Epo promoter activity.<sup>9</sup>

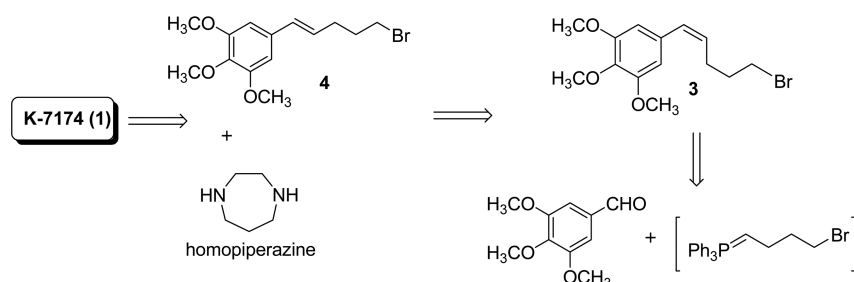
Since, the pioneer investigation of K-7174,<sup>10</sup> as a cell adhesive inhibitory agents, or a pharmaceutical for the treatment of pathological conditions attributed to cell adhesion or cellular infiltration (*e.g.* anti-rheumatic agent, anti-allergic agent, or cancer metastasis inhibitory agent), it has attracted a great deal of interest from the chemical and biological communities. Despite of its interesting biological properties, the synthesis of K-7174 has only appeared in a single patent.<sup>10</sup> In the existing synthetic route, the preparation of requisite aryl alkenyl bromide **4** is neither reported in literature, nor commercially available. Thus, the new and efficient routes are still required to fulfill the demands of the biologists to make it available in large quantities. The simple structural feature coupled with the interesting biological activity prompted us to develop a short and practical synthesis of K-7174 using straightforward synthetic manipulations.

### Results and Discussion

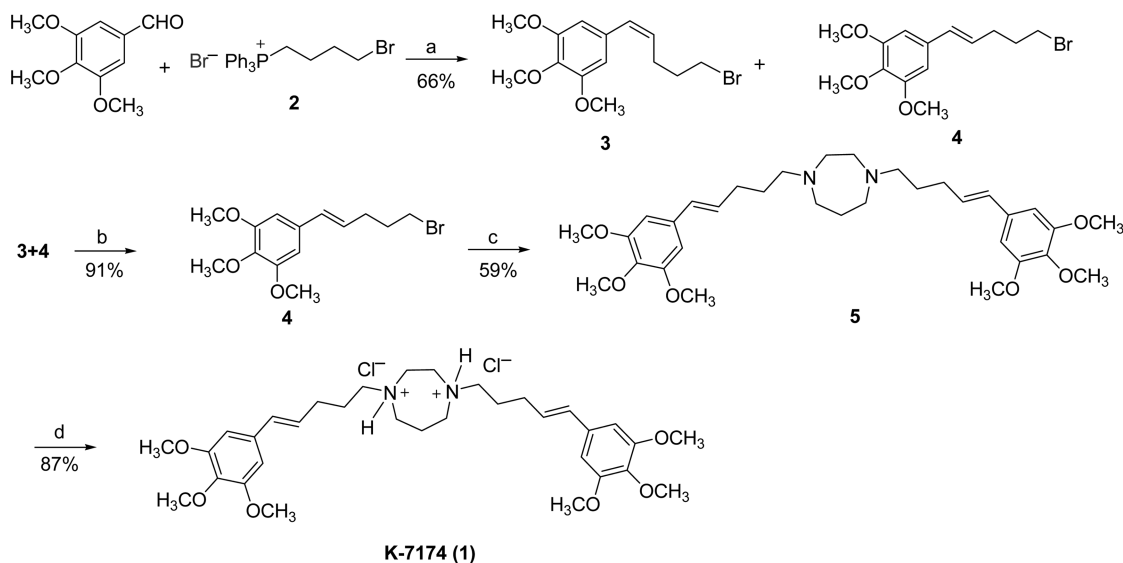
Scheme 1 illustrates the retrosynthetic analysis of K-7174 (**1**). K-7174 (**1**) might be synthesized from bis-alkylation of homopiperazine with *E*-alkenyl bromide **4**, which is isomeri-



**Figure 1.** K-7174, a cell adhesive inhibitor.



**Scheme 1.** Retrosynthetic analysis of K-7174 (**1**).



**Scheme 2.** Reagent and conditions: (a)  $\text{K}_2\text{CO}_3$ , THF, reflux, 48 h; (b)  $\text{I}_2$ ,  $\text{CH}_3\text{CN}$ , reflux, 2 h; (c) homopiperazine,  $\text{K}_2\text{CO}_3$ , KI,  $\text{CH}_3\text{CN}$ , reflux, 7 h; (d) 4 M HCl/dioxane, 3 h, 0 °C to rt.

zed from *Z*-alkenyl bromide **3**. The compound **3** could be derived from the Wittig reaction of the corresponding aldehyde with unstabilized phosphorous ylide.

Our approach to **1** using Wittig olefination is depicted in Scheme 2.

The phosphonium salt **2** was readily synthesized in large scale from 1,4-dibromobutane<sup>11</sup> with 1 equiv of  $\text{PPh}_3$  in toluene and can be stored indefinitely. The instability of phosphorane generated from salt **2** in the presence of strong base, restricted the application of direct Wittig salt **2** in synthetic endeavors.<sup>12</sup> Hence, the corresponding phosphorane was generated *in situ* by using mild phase transfer condition (solid  $\text{K}_2\text{CO}_3$ ) and trapping with 3,4,5-trimethoxybenzaldehyde furnished inseparable mixture of *cis* olefin **3** and *trans* olefin **4** in 66% yield and 3:1 ratio. It is well known in the literature that non-stabilized triphenylphosphorus ylides generally react with aldehyde to afford mainly *Z*-alkenes.<sup>13</sup> However, the high *E*-selectivity in the reaction of non-stabilized phosphorus ylides can be induced by method of Schlosser, which entails metalation of Wittig intermediate (betaine) at low temperature to give lithio- $\beta$ -oxido ylide, whereupon they react with aldehyde to produce a preponderance of *E*-alkene.<sup>14</sup> Hence, to increase the *E*-stereoselectivity, the reaction was carried out in the presence of  $\text{LiBr}$ <sup>15</sup> along with base, but we didn't succeed in improv-

ing desired *E*-selectivity in double bond formation. Furthermore, the Wittig reaction of salt **2** using solid  $\text{KOH}$ <sup>12</sup> gave similar result as previous reaction used solid  $\text{K}_2\text{CO}_3$ . Subsequently, we thought of utilizing olefin isomerization approach to prepare *trans* olefin **4**. The iodine catalyzed *cis-trans* isomerization of olefins, in particular *cis-trans* isomerization of stilbene and its derivatives is well precedent in the literature.<sup>16</sup> Thus, the treatment of a mixture of *cis* olefin **3** and *trans* olefin **4** with catalytic amount of  $\text{I}_2$  (10 mol %) in  $\text{CH}_3\text{CN}$  at 90 °C produced exclusively *trans* olefin **4** within 2 h. The *cis* and *trans* configuration of the alkenes **3** and **4** were easily confirmed by measuring the characteristic coupling constants of olefinic protons in  $^1\text{H}$  NMR spectroscopy which appeared as doublets at  $\delta$  6.40 ( $J = 11.6$  Hz) and 6.37 ( $J = 15.6$  Hz), respectively. With the sufficient amount of *trans* olefin **4** in hand, we subjected it to *bis-N*-alkylation with homopiperazine. Initially, we tried alkylation using  $\text{KI}/\text{K}_2\text{CO}_3/\text{DMF}$  employing reported method<sup>10</sup> which gave the expected product **5** in low yield (32%). However, the same reaction using  $\text{KI}/\text{K}_2\text{CO}_3/\text{CH}_3\text{CN}$  under refluxing conditions afforded diamine **5** in 59% yield. Finally, K-7174 (**1**) was prepared by the treatment **5** with 4 M HCl in dioxane.

In summary, an efficient new synthesis of the promising anti-inflammatory agent K-7174 (**1**) has been completed.

Notable transformations include the construction of *trans* double bond *via* Wittig olefination and iodine catalyzed isomerization. Overall, K-7174 (**1**) was prepared in four steps and 31% overall yield. It is believed that the present approach offers a new and simple access to K-7174, which could provide the foundation for a long-term manufacturing-scale supply of K-7174.

### Experimental Section

**General Methods.**  $^1\text{H}$  NMR spectra ( $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ , or  $\text{DMSO}-d_6$ ) were recorded on Varian Unity Inova 400 MHz. Chemical shifts are reported in parts per million ( $\delta$ ) units relative to the solvent peak. The  $^1\text{H}$  NMR data are reported as peak multiplicities: s for singlet; d for doublet; dd for doublet of doublets; t for triplet; pseudo t for pseudo triplet; brs for broad singlet; and m for multiplet. Coupling constants were reported in Hertz.  $^{13}\text{C}$  NMR spectra ( $\text{CDCl}_3$ ,  $\text{CD}_3\text{OD}$ , or  $\text{DMSO}-d_6$ ) were recorded on Varian Unity Inova 100 MHz. The chemical shifts are reported as ppm ( $\delta$ ) relative to the solvent peak. Mass spectra were recorded on Agilent Technologies 6220 Accurate-Mass TOF LC/MS spectrometer. Melting points were measured on IA9100 made by Barnstead. These are uncorrected. Reactions were checked with TLC (Merck precoated 60F254 plates). Spots were detected by viewing under a UV light, coloring with charring after dipping in anisaldehyde solution with acetic acid and sulfuric acid and methanol. Column chromatography were performed on silica gel 60 (230-400 mesh, Merck). Reagents were purchased from Aldrich Chemical Company. Solvents were obtained from local suppliers. All the anhydrous solvents were distilled over  $\text{CaH}_2$ ,  $\text{P}_2\text{O}_5$ , or  $\text{Na/benzophenone}$  prior to the reaction.

**(4-Bromobutyl)triphenylphosphonium Bromide (2).** A solution of triphenylphosphine (30.00 g, 0.11 mole) and 1,4-dibromobutane (24.69 g, 0.11 mol) in xylene (150 mL) was stirred under reflux for 24 h. The crude solid material was filtered and washed with  $\text{Et}_2\text{O}$  ( $3 \times 100$  mL) to give white solid (50.00 g, 92%) which was dried under high vacuum prior to use.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.67-7.90 (m, 15 H), 3.93-4.00 (m, 2 H), 3.60 (t, 2 H,  $J = 6.0$  Hz), 2.28-2.35 (m, 2 H), 1.80-1.86 (m, 2 H).

**(Z)-5-(4-Bromobut-1-enyl)-1,2,3-trimethoxybenzene (3) and (E)-5-(4-Bromobut-1-enyl)-1,2,3-trimethoxybenzene (4).** A mixture of (4-bromobutyl)triphenylphosphonium bromide **2** (63.00 g, 0.13 mol), 3,4,5-trimethoxybenzaldehyde (23.50 g, 0.12 mol), and potassium carbonate (8.87 g, 0.16 mol) in anhydrous THF (250 mL) was stirred under reflux for 48 h. The reaction mixture was cooled to room temperature, filtered, and washed with EtOAc. The combined filtrates were evaporated and dissolved in EtOAc (200 mL). The organic layer was washed with water (100 mL), brine (100 mL), dried over anhydrous  $\text{MgSO}_4$ , filtered, and evaporated. The crude residue was purified by silica gel column chromatography (8% EtOAc in hexanes) to give a 3:1 mixture (46.0 g, 66%) of *Z*-olefin **3** and *E*-olefin **4**.

A solution of a mixture (12.0 g, 0.038 mol) of *Z*-olefin **3**

and *E*-olefin **4** and catalytic amount of iodine (10 mol %) in  $\text{CH}_3\text{CN}$  (250 mL) was stirred under reflux for 2 h. The reaction mixture was cooled to room temperature, and diluted with EtOAc (200 mL). The organic layer was separated, washed with sodium thiosulfate solution ( $2 \times 100$  mL), dried over anhydrous  $\text{MgSO}_4$ , filtered, and evaporated. The pale yellow liquid was purified by silica gel column chromatography (8% EtOAc in hexanes) to give *trans* isomer **4** exclusively as colorless sticky liquid (10.9 g, 91%).

**Z-Olefin 3:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.48 (s, 2 H), 6.40 (d, 1 H,  $J = 11.6$  Hz), 5.34-5.60 (m, 1 H), 3.85 (s, 6 H), 3.84 (s, 3 H), 3.42 (t, 2 H,  $J = 6.8$  Hz), 2.47-2.53 (m, 2 H), 1.97-2.04 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  153.1, 137.2, 133.1, 130.4, 130.3, 106.1, 61.0, 56.3, 33.3, 32.9, 27.4.

**E-Olefin 4:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.57 (s, 2 H), 6.37 (d, 1 H,  $J = 15.6$  Hz), 6.04-6.11 (m, 1 H), 3.87 (s, 6 H), 3.84 (s, 3 H), 3.46 (t, 2 H,  $J = 6.8$  Hz), 2.34-2.40 (m, 2 H), 2.00-2.07 (m, 2 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  153.5, 137.7, 133.4, 131.4, 128.2, 103.3, 61.1, 56.3, 33.4, 32.4, 31.4; ESI-MS:  $m/z$  [ $\text{M} + \text{Na}$ ] $^+$  calcd for  $\text{C}_{14}\text{H}_{19}\text{BrNaO}_3$ , 337.0410; found, 337.0416.

**1,4-Bis((E)-5-(3,4,5-trimethoxyphenyl)pent-4-enyl)-1,4-diazepane (5).** A suspension of (*E*)-5-(4-bromobut-1-enyl)-1,2,3-trimethoxybenzene (**4**, 14.1 g, 0.04 mol), homopiperazine (2.24 g, 0.02 mol), potassium carbonate (6.19 g, 0.04 mol), and potassium iodide (8.90 g, 0.05 mol) in  $\text{CH}_3\text{CN}$  (200 mL) were refluxed for 7 h. The reaction mixture was diluted with EtOAc (150 mL), the insoluble material was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was partitioned between a saturated  $\text{NaHCO}_3$  solution (150 mL) and EtOAc (300 mL) and the organic layer was washed with brine (100 mL), dried over anhydrous  $\text{MgSO}_4$ , filtered, and evaporated to give the sticky liquid, which was purified by using silica gel (silica was neutralized with 1% ammonia solution) column chromatography (6% MeOH in  $\text{CH}_2\text{Cl}_2$ ) to give **5** (14.80 g, 59%) as pale yellow liquid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.66 (s, 4 H), 6.35 (d, 2 H,  $J = 16.0$  Hz), 6.16-6.24 (m, 2 H), 3.83 (s, 12 H), 3.74 (s, 6 H), 2.75-2.78 (m, 8 H), 2.53-2.57 (m, 4 H), 2.20-2.25 (m, 4 H), 1.83-1.86 (m, 2 H), 1.64-1.72 (m, 4 H); ESI-MS:  $m/z$  [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{33}\text{H}_{49}\text{N}_2\text{O}_6$ , 569.3585; found, 569.3589.

**1,4-Bis((E)-5-(3,4,5-trimethoxyphenyl)pent-4-enyl)-1,4-diazepane Dihydrochloride salt (1, K-7174).** To a stirred solution of **5** (4.00 g, 7.0 mmol) in dioxane (80 mL) was added 4 M HCl/dioxane (12 mL) at 0 °C and the reaction was stirred at room temperature for 3 h. The solvent was evaporated to give gummy liquid which was triturated with  $\text{Et}_2\text{O}$  (100 mL) at room temperature for 1 h to give **1** (3.93, 87%) as a white solid: mp 104-105 °C [lit<sup>10</sup> mp 103 °C];  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  11.50 (br s, 1 H,  $\text{D}_2\text{O}$  exchangeable), 11.14 (br s, 1 H,  $\text{D}_2\text{O}$  exchangeable), 6.70 (s, 4 H), 6.38 (d, 2 H,  $J = 16.0$  Hz), 6.20-6.28 (m, 2 H), 3.78 (s, 12 H), 3.64 (s, 6 H), 3.34-3.37 (m, 12 H), 2.21-2.26 (m, 6 H), 1.88-1.91 (m, 4 H).

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