Improved Synthesis of RG-14893, a High-Affinity Leukotriene B_4 Receptor Antagonist, via a Photochemical Wolff Rearrangement

Israil Pendrak* and Pamela A. Chambers

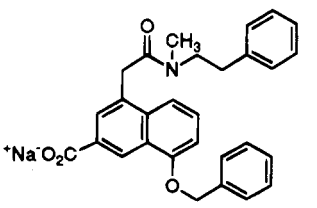
Department of Medicinal Chemistry, SmithKline Beecham Pharmaceuticals, P.O. Box 1539, King of Prussia, Pennsylvania 19406

Received January 9, 1995

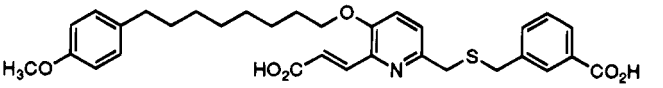
In support of our discovery effort in the leukotriene B_4 receptor antagonist area, we required quantities of the Rhone-Polenc Rorer leukotriene B_4 receptor antagonist, RG-14893 (**1**, Figure 1), for comparison in in vivo assays with our lead compound SB 201993 (**2**).[1] Following published procedures,[2,3] we prepared triflate **3** which was subsequently converted into the hydroxyethyl compound **4** via palladium-catalyzed coupling with tributylvinyltin, followed by hydroboration–oxidation (Scheme 1). However, in our hands, conversion of **4** to the penultimate carboxylic acid **5** by Jones oxidation resulted only in trace amounts of **5**. Furthermore, various other attempts to prepare sufficient quantities of the carboxylic acid **5** suitable for large scale preparation of **1** were unsatisfactory. Therefore, we designed an alternate synthesis for **1**.

Results and Discussion

Due to our unsuccessful attempts to oxidize **4** to carboxylic acid **5**, we decided to investigate a route to **1** that circumvented the oxidative step. It occurred to us that one such approach potentially suited for this synthesis is the Arndt–Eistert synthesis[4] in which the homologation of a carboxylic acid or the rearrangement of a methyl ketone occurs through a common diazo ketone intermediate. However, this application will lead to two ester functionalities on the molecule, selective hydrolysis of which would likely present a problem. For this reason, it would be desirable to go directly to the amide at the homologation step. A literature precedent which describes a Photo-Wolff rearrangement of a diazo ketone to generate an amide[5] suggested an approach to accomplish this.



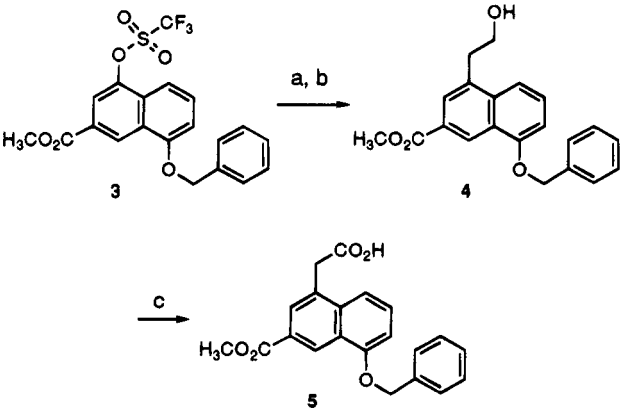
(1) RG-14893



(2) SB-201993

Figure 1.

Scheme 1



[a] (a) Tributylvinyltin, LiCl, $PdCl_2(PPh_3)_2$, DMF, 80%; (b) (1) 9-BBN, THF; (2) H_2O_2, NaOH, 52%; (c) Jones' reagent, acetone, 5%.

The successful synthesis of RG-14893 (**1**) by application of the Photo-Wolff rearrangement is shown in Scheme 2. Triflate **3** was converted to ketone **6** in two steps via a palladium-catalyzed Heck coupling reaction[6] using butyl vinyl ether to give the corresponding enol vinyl ether; hydrolysis of the enol vinyl ether afforded the ketone **6**. Ketone **6** was converted to the α-diazo ketone **7** in two steps by the method of Danheiser et al.;[7] ketone was activated as the α-trifluoroacetyl derivative, followed by reaction with methanesulfonyl azide to produce diazo ketone **7**. Photo-Wolff rearrangement of the diazo ketone **7** (Pyrex, standard mercury lamp) in the presence of methylphenethylamine afforded compound **8** in 87% yield. Hydrolysis of methyl ester gave the title compound **1**.

In conclusion, the synthesis of RG-14893 (**1**) was achieved in five steps from triflate **3** in 24% overall yield. In addition, this synthetic route can be used for large scale synthesis of **1**. Finally, the use of this Photo-Wolff

(1) (a) Daines, R. A.; Chambers, P. A.; Pendrak, I.; Jakas, D. R.; Sarau, H. M.; Foley, J. J.; Schmidt, D. B.; Griswold, D. E.; Martin, L. D.; Kingbury, W. D. (*E*)-3-[[[[6-(2-Carboxyethynyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]benzoic Acid: A Novel High Affinity Leukotriene B_4 Receptor Antagonist. *J. Med. Chem.* 1993, *36*, 2703–2705. (b) Daines, R. A.; Chambers, P. A.; Eggleston, D. S.; Foley, J. J.; Griswold, D. E.; Haltiwanger, R. C.; Jakas, D. R.; Kingbury, W. D.; Martin, L. D.; Pendrak, I.; Schmidt, D. B.; Tzimas, M. N.; Sarau, H. M. (*E*)-3-[[[[6-(2-Carboxyethynyl)-5-[[8-(4-methoxyphenyl)octyl]oxy]-2-pyridinyl]methyl]thio]methyl]benzoic Acid and Related Compounds: High Affinity Leukotriene B_4 Receptor Antagonists. *J. Med. Chem.* **1994**, *37*, 3327–3336.

(2) Huang, F. C.; Chan, W. K.; Warus, J. D.; Morrissette, M. M.; Moriarty, K. J.; Chang, M. N.; Travis, J. J.; Mitchell, L. S.; Nuss, G. W.; Sutherland, C. A. 4-[2-[Methyl(2-phenethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylic Acid: A High Affinity, Competitive, Orally Active Leukotriene B_4 Receptor Antagonist. *J. Med. Chem.* **1992**, *35*, 4253–4255.

(3) Huang, F. C.; Chan, W. K.; Sutherland, C. A.; Galemmo, R., Jr. Substituted Bicyclic Aryl Compounds Exhibiting Selective Leukotriene B_4 Antagonist Activity. Derwent Patent Publication WO-9204321A, 1992.

(4) Bachmann; Struve. *Organic Reactions;* John Wiley and Sons, Inc.: New York, 1942; Vol. 1, *p* 38–62.

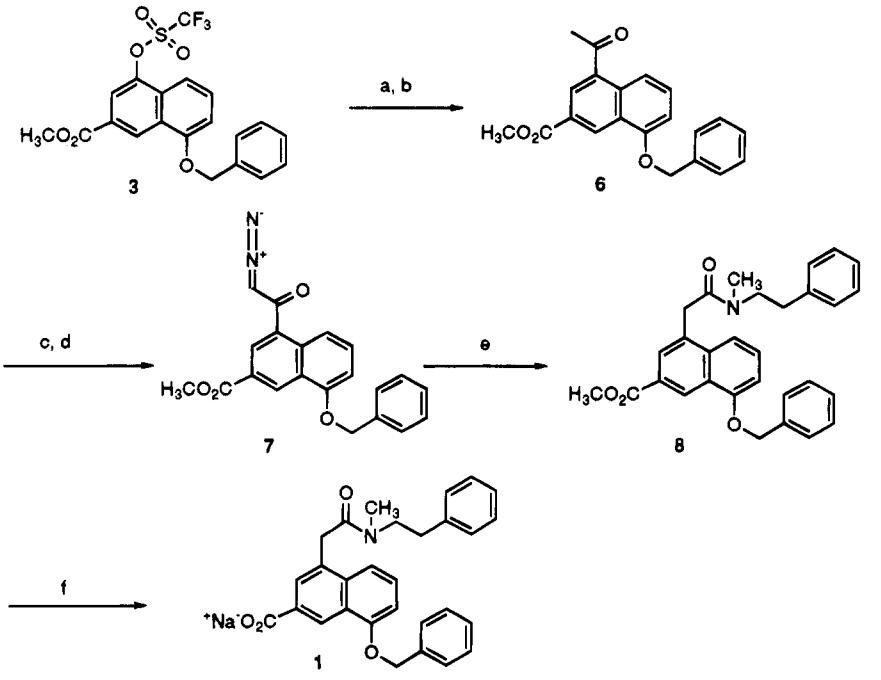
(5) Bradshaw, J. S.; Carlock, J. T.; Stanovnik, B.; Tisler, M. A Noteworthy Improvement of the 3-Diazo-4-oxo-3,4-dihydroquinoline Photosynthesis of Indole-3-carboxamides. *J. Heterocycl. Chem.* **1977**, *14*, 519–520.

(6) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingbury, W. D. Synthesis and Anti-HSV Activity of A-Ring Deleted Mappicine Ketone Analog. *J. Org. Chem.* **1994**, *59*, 2623–2625.

(7) Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. An Improved Method for the Synthesis of α-Diazo Ketones. *J. Org. Chem.* **1990**, *55*, 1959–1964.

0022-3263/95/1960-3249$09.00/0

Scheme 2



[a] (a) Butyl vinyl ether, Et_3N, $Pd(OAc)_2$, dppp, DMF; (b) AcOH, HCl, rt, 84%, for two steps; (c) $LiN(SiCH_3)_2$, THF, −78 °C, trifluoroethyl fluoroacetate; (d) $CH_3SO_2N_3$, Et_3N, acetonitrile, H_2O, 37%, for two steps; (e) hν, [methyl(phenethyl)]amine 87%; (f) aqueous NaOH, THF, CH_3OH, 89%.

rearrangement appears to be general, permitting the synthesis of both primary and secondary amides.

Experimental Section

General Procedures. Melting points were determined on a capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained in $CDCl_3$ solvent unless otherwise stated; all values are reported in parts per million (δ) from $(CH_3)_4Si$ unless otherwise stated. Elemental analyses were performed in the Analytical and Physical Chemistry Department of SmithKline Beecham Pharmaceuticals. Electrospray (ES) mass spectra were obtained by the Physical and Structural Chemistry Department at SmithKline Beecham Pharmaceuticals. Analytical thin-layer chromatography (TLC) was carried out with silica gel GF plates. Column chromatography was performed with silica gel. Compounds were named following IUPAC rules.

Methyl 4-Acetyl-8-(phenylmethoxy)-2-naphthalenecarboxylate (6). To a solution of methyl 8-(phenylmethoxy)-4-[[(trifluoromethyl)sulfonyl]oxy]-2-naphthalenecarboxylate (**3**)[2,3] (3 g, 6.8 mmol) in DMF (30 mL) were added triethylamine (1.9 mL, 13.6 mmol) and n-butyl vinyl ether (3.5 mL, 27.2 mmol). To the resulting mixture was added $Pd(OAc)_2$ (90 mg, 6% mol) along with 1,3-bis(diphenylphosphino)propane (0.162 g, 6% mol). The resulting mixture was stirred at 60 °C for 24 h. The reaction mixture was concentrated under vacuum, and the residue was purified by flash column chromatography (silica, 30% EtOAc:hexane) to give methyl 4-(1-butoxyvinyl)-8-(phenylmethoxy)-2-naphthalenecarboxylate as an oil (2.6 g, 100%).

To a solution of 4-(1-butoxyvinyl)-8-(phenylmethoxy)-2-naphthalenecarboxylate (2.6 g, 6.8 mmol) in glacial acetic acid (15 mL) was added 3 N HCl (10 mL), and the reaction mixture was stirred at room temperature for 1 h. The precipitated yellow solid was filtered, washed with H_2O, and dried in vacuo to give **6** as a yellow solid (1.91 g, 84%): ^1H NMR δ 9.27 (s, 1H), 8.52 (s, 1H), 8.30 (d, 1H), 7.60 (t, 1H, J = 7 Hz), 7.52−7.26 (m, 5H), 6.99 (d, 1H, J = 7 Hz), 5.31 (s, 2H), 4.0 (s, 3H), 2.79 (s, 3H); MS (ES) 335 $(M + H)^+$. Anal. Calcd for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.76; H, 5.60.

Methyl 4-(Diazoacetyl)-8-(phenylmethoxy)-2-naphthalenecarboxylate (7). A 125 mL three-necked round-bottomed flask equipped with a rubber septum, an argon inlet adapter, and a 50 mL pressure-equalizing addition funnel was charged with a solution of 1,1,1,3,3,3-hexamethyldisilazane (1.32 mL, 6.2 mmol) in THF (20 mL) and then cooled to 0 °C while n-butyllithium solution (2.5 M in hexane, 2.5 mL, 6.2 mmol) was added rapidly dropwise. After 10 min, the resulting solution was cooled to −78 °C and a solution of ketone **6** (1.9 g, 5.68 mmol) in THF (20 mL) was added dropwise over 15 min. The reaction mixture was stirred at −78 °C for 30 min, and then 2,2,2-trifluoroethyl trifluoroacetate (0.91 mL, 6.81 mmol) was added rapidly by syringe in one portion. After 10 min, the reaction mixture was poured into a separatory funnel containing 30 mL of 5% aqueous HCl solution and 40 mL of Et_2O. The aqueous phase was extracted with two 30 mL portions of Et_2O, and the combined organic phases were then washed with brine (30 mL) and concentrated under reduced pressure to give a green solid. The resulting solid was immediately dissolved in CH_3CN (20 mL) and the solution transfered to a 125 mL three-necked round-bottomed flask equipped with a rubber septum, as argon inlet adapter, and a 50 mL pressure-equalizing addition funnel. Water (0.1 mL, 5.5 mmol) and Et_3N (1.1 mL, 7.95 mmol) were added, and a solution of methanesulfonyl azide (0.96 g, 0.69 mL, 7.95 mmol) in CH_3CN (20 mL) was added rapidly. The resulting mixture was stirred at room temperature for 3 h and then concentrated to a volume of ca. 20 mL. The residue was diluted with Et_2O (30 mL), washed with 10% aqueous NaOH solution and brine, and dried ($MgSO_4$). The reaction mixture was concentrated under vacuum, and the residue was purified by flash column chromatography (silica, 0−50% EtOAc:hexane) to to give **7** as a solid (1 g, 49%): ^1H NMR δ 9.27 (s, 1H), 8.27 (s, 1H), 8.10 (br s, 1H), 7.60 (t, 1H, J = 7 Hz), 7.52−7.35 (m, 5H), 6.99 (d, J = 7 Hz, 1H), 5.85 (br s, 1H), 5.35 (s, 2H), 4.0 (s, 3H); MS (ES) 361 $(M + H)^+$.

Methyl 4-[2-[Methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylate (8). A Pyrex bottle was charged with a solution of azide **7** (0.77 g, 2.13 mmol) and methylphenethylamine (0.87 mL, 5.98 mmol) in toluene (120 mL). The resulting solution was irradiated with a Hanovia mercury lamp for 5 h. The reaction mixture was concentrated under vacuum, and the residue was purified by flash column chromatography (silica, 10−60% EtOAc:hexane) to give **8** as an oil (0.87 g, 87%): ^1H NMR (mixture of rotomers) δ 9.09, 9.02 (two s, 1H), 7.99, 7.78 (two s, 1H), 7.52−7.15 (m, 12H), 6.91 (two d, J = 5 Hz, 1H), 5.31, 5.29 (two s, 2H), 4.12, 3.78 (two s, 2H),

3.95, 3.96 (two s, 3H), 3.67 (m, 2H), 3.08, 2.98 (two t, J = 3 Hz, 3H), 2.92, 2.88 (two t, J = 3 Hz, 2H); MS (ES) 468 (M + H). Anal. Calcd for $C_{30}H_{29}NO_4$: C, 77.07; H, 6.25; N, 3.00. Found: C, 76.99; H, 6.40; N, 2.81.

Sodium 4-[2-[Methyl(2-phenylethyl)amino]-2-oxoethyl]-8-(phenylmethoxy)-2-naphthalenecarboxylate (1). To a solution of **8** (0.87 g, 1.86 mmol) in methanol (20 mL), THF (20 mL), and H_2O (10 mL) was added NaOH (2 M solution in H_2O, 2.8 mL, 5.5 mmol). The reaction solution was stirred at room temperature for 24 h and concentrated under vacuum, and the residue was purified by reversed phase medium pressure liquid chromatography (C_{18} ODS-3 silica, 0–60% MeOH:H_2O) to give after lyophilization **1** as a white solid (0.75 g, 82%): ^{1}H NMR (mixture of rotomers) (CD_3OD) δ 9.09, 9.02 (two s, 1H), 7.99, 7.78 (two s, 1H), 7.52–7.15 (m, 12H), 6.91 (two d, J = 5 Hz, 1H), 5.31, 5.29 (two s, 2H), 4.12, 3.78 (two s, 2H), 3.67 (m, 2H), 3.08, 2.98 (two t, J = 3 Hz, 3H), 2.92, 2.88 (two t, J = 3 Hz, 2H). Anal. Calcd for $C_{29}H_{26}NO_4Na{\cdot}H_2O$: C, 70.58; H, 5.72; N, 2.84. Found: C, 70.83; H, 5.63; N, 3.10.

Supplementary Material Available: ^{1}H NMR spectrum of **7** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950071U