The First Total Synthesis of Galloyl Tyramine

Nisar Ullah

Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia

Reprint requests to Professor Nisar Ullah.
Fax: + 966 3 860 4277. E-mail: nullah@kfupm.edu.sa

Z. Naturforsch. **2009**, *64b,* 464 – 466;
received December 17, 2008

The first total synthesis of galloyl tyramine, an inhibitor of Pim2 kinase was accomplished in an overall high-yield reaction sequence.

Key words: Total Synthesis, Natural Product, Antitumor Agent

Introduction

The Pim family of cytoplasmic serine/threonine kinases comprises three proto-oncogenes, Pim1, Pim2, and Pim3. With specificity towards phosphorylation on serine/threonine residues, this distinct class of kinases collectively contributes to the control of programmed cell death and cellular metabolism [1, 2]. There is more than 53 % identity in the amino-acid level among the three family members with each having a somewhat different pattern of tissue distribution [3]. Because these kinases phosphorylate some of the same substrates, there appears to be a certain level of redundancy in their function. Mice with a deficiency for all Pim kinases display a significant reduction in body size and impaired growth factor signaling in hematopoietic cells, suggesting that physiologically the Pim kinases are important in growth factor signaling [4]. Deregulated Pim kinase expression has been reported in a variety of myeloid and lymphoblastic leukemias [5], in other cancers such as prostate cancer, B cell lymphoma, chronic lymphocytic leukemia, acute myelogenous leukemia [6], and also its implication in Moloney murine leukemia virus-induced lymphomas [3, 7]. Thus, the discovery of Pim kinases inhibitors has a good potential to find applications in the treatment of various diseases including cancer, inflammatory disorders, and ischemic diseases [6].

Recently bioassay-guided fractionation of an organic extract of the rainforest tree *Cupaniopsis macropetala* Radlk. (Sapindaceae) has resulted in the isolation of a new alkaloid, galloyl tyramine **1**, an inhibitor of the Pim2 kinase with IC50 values of 161 [8]. As a part of our ongoing research in the total synthesis of bio-active natural products [9], we now wish to report the first total synthesis of galloyl tyramine **1**.

Results and Discussion

Our synthetic strategy (Scheme 1) commenced with the synthesis of perbenzylated gallic acid **4**, which was prepared by adopting a known procedure with some modifications. Benzylation of methyl gallate **2** with benzyl bromide in DMF [10], followed by hydrolysis of the ester by LiOH to produce **4**, was not only high-yielding (96 %) but also no additional workup was necessary as opposed to usage of KOH as a base [10]. The coupling of acid **4** with *N-t*-Boc-tyramine **6** [11] using dicyclohexylcarbodiimide yielded a complex mixture of products with no trace of the desired carbamate **7**.

In another attempt the acid **4** was transformed to the corresponding acid chloride **5**, which in turn was added to a stirred solution of *N-t*-Boc-tyramine **6** in CH_2Cl_2 and Et_3N at r. t. rendering the desired carbamate **7** in 70 % yield after column chromatography purification. Hydrogenation of compound **7** generated the intermediate **8**, which in turn was deprotected by the action of trifluoroacetic acid in CH_2Cl_2 to produce the desired galloyl tyramine **1** in 71 % yield (Scheme 1).

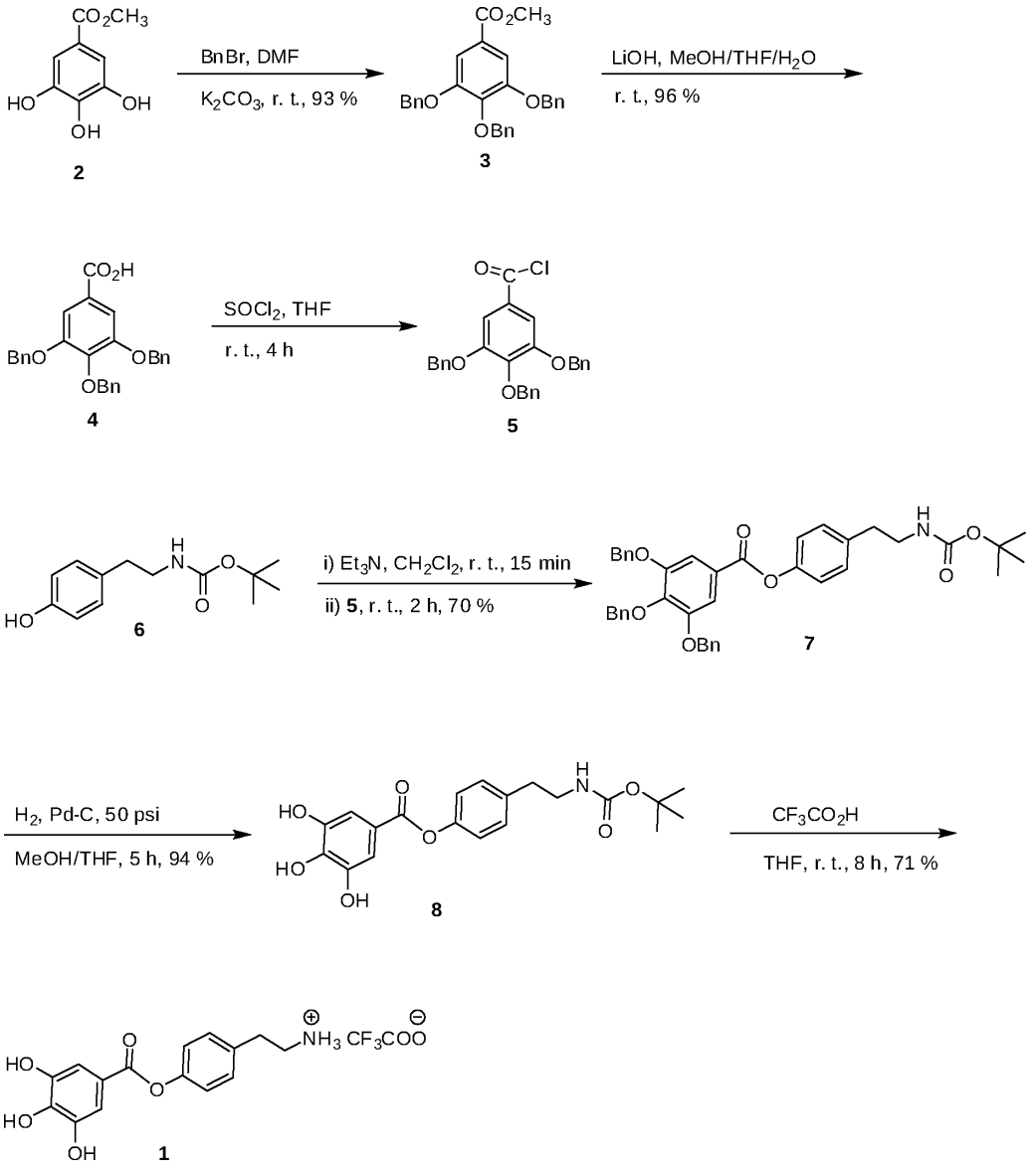
Conclusion

In conclusion we have accomplished the efficient first total synthesis of galloyl tyramine **1**, an inhibitor of Pim2 kinase in an overall 47 % yield from **4** and **6**.

Experimental Section

*3,4,5-Tris(benzyloxy)benzoic acid (**4**)*

Ester **3** (0.8 g, 1.76 mmol) was dissolved in a 1 : 2 : 1 mixture of 16 mL of MeOH, THF and H_2O, followed by the addition of $LiOH{\cdot}H_2O$ (0.22 g, 5.28 mmol), and the reaction mixture was stirred for 12 h at r. t. The mixture was concentrated *in vacuo* to remove the organic solvents, 6 N HCl (20 mL) was added, and the resulting white crystalline material of **4** was filtered, washed with H_2O (3 mL) and dried under vacuum to get acid **4** as a white solid, whose physical and spectral data were identical to the reported ones [10].



Scheme 1. Synthesis of galloyl tyramine (**1**).

*tert-Butyl 4-[3,4,5-tri(benzyloxy)benzoyloxy]phenethylcarbamate (**7**)*

To a solution of acid **4** (0.3 g, 0.68 mmol) in THF (10 mL) was added $SOCl_2$ (0.2 mL, 2.74 mmol), and the mixture was stirred for 4 h at r. t. and evaporated to dryness to afford the acid chloride **5**. In another flask carbamate **6** (0.13 g, 0.57 mmol), was dissolved in CH_2Cl_2 (5 mL), and Et_3N (0.19 mL) was added, and the mixture was stirred for 15 min at r. t., followed by the drop-by-drop addition of the acid chloride **5**, dissolved in 2 mL of CH_2Cl_2. The reaction mixture was stirred at r. t. for 2 h, the solvents were evaporated, and the brown oily material was resolved on a silica column eluting with hexanes-ethyl acetate = 8 : 2 to afford 0.26 g (70 %) of **7** as an off-white solid. M. p. 94 – 95 °C. – IR (neat): ν = 3367, 2932, 1728, 1682, 1586, 1506, 1331, 1181, 1112, 951, 739 cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, $COOC(CH_3)_3$), 2.81 (t, J = 7.4 Hz, 2 H, 2-H), 3.38 (m, 2 H, 1-H), 5.15 (s, 6 H, CH_2Ph), 7.11 (d, J = 8.2 Hz, 2 H, 5-H, 7-H), 7.27 – 7.23 (m, 4 H, aromatic H), 7.44 – 7.32 (m, 14 H, aromatic H), 7.52 (s, 2 H, 3′-H, 7′-H). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 28.41 ($COOC(CH_3)_3$), 35.60

(C-2), 41.73 (C-1), 71.25 (CH_2Ph), 75.15 (CH_2Ph), 79.26 (COOC(CH_3)$_3$), 109.58 (C-3′, C-7′), 121.75 (C-5, C-7), 124.43 (C-2′), 127.56 (C_{arom}), 128.0 (C_{arom}), 128.10 (V), 128.21 (C_{arom}), 128.54 (C_{arom}), 129.80 (C-4, C-8), 136.52 (C_q-aryl), 136.69 (C_q-aryl), 137.33 (C-3), 142.93 (C-5′), 149.50 (C-6), 152.63 (C-4′, C-6′), 155.88 (COOC(CH_3)$_3$), 164.81 (C-1′). – $C_{41}H_{41}NO_7$ (659.29): calcd. C 74.64, H 6.26, N 2.12; found C 74.60, H 6.28, N 2.09.

*tert-Butyl 4-[3,4,5-tri(hydroxy)benzoyloxy]phenethylcarbamate (**8**)*

To a solution of compound **7** (0.2 g, 0.30 mmol) in a 2 : 1 mixture of THF and MeOH (15 mL) was added 0.04 g of Pd/C (10 %), and the reaction mixture was subjected to hydrogenation in a Parr apparatus at 50 psi for 5 h. The mixture was filtered through a pad of celite, and the filtrate was concentrated under vacuum and loaded on a silica column, eluting with hexanes-ethyl acetate = 3 : 7 and then changing to ethyl acetate (100 %) to afford 0.11 g (94 %) of **8** as a white foam. – IR (neat): ν = 3382, 2966, 1701, 1685, 1318, 1190, 1164, 1033 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.44 (s, 9 H, COOC(CH_3)$_3$), 2.78 (t, J = 7.3 Hz, 2 H, 2-H), 3.21 (m, 2 H, 1-H), 6.97 (m, 1 H, NH COOC(CH_3)$_3$), 7.15 (s, 2 H, 3′-H, 7′-H), 7.18 (d, J = 8.2 Hz, 2 H, 5-H, 7-H), 7.31 (d, J = 8.2 Hz, 2 H, 4-H, 8-H), 9.20 (s, 1 H, OH-5′), 9.47 (s, 2 H, OH-4′, OH-6′). – ^{13}C NMR (125.7 MHz, [D$_6$]DMSO): δ = 28.28 (COOC(CH_3)$_3$), 34.77 (C-2), 41.49 (C-1), 77.55 (COOC(CH_3)$_3$), 109.10 (C-3′, C-7′), 118.33 (C-2′), 121.74 (C-5, C-7), 129.59 (C-4, C-8), 136.85 (C-3), 139.20 (C-5′), 145.74 (C-4′, C-6′), 149.14 (C-6), 155.55 (COOC(CH_3)$_3$), 164.68 (C-1′). – $C_{20}H_{23}NO_7$ (389.15): calcd. C 61.69, H 5.96, N 3.60; found C 61.66, H 5.99, N 3.56.

*Galloyl tyramine (**1**)*

Compound **8** (0.06 g, 0.15 mmol) was dissolved in THF (5 mL) followed by the addition of trifluoroacetic acid (1 mL), and the mixture was stirred at r. t. for 8 h. The solvents were evaporated under vacuum, and the brown thick oily material was washed thoroughly with CH_2Cl_2 to produce 0.043 g (71 %) of **1**. The spectral data of our synthetic **1** were identical to those of the natural material [8].

[1] S. Holder, M. Zemskova, C. Zhang, M. Tabrizizad, R. Bremer, J. W. Neidigh, M. B. Lilly, *Mol. Cancer Ther*. **2007**, *6*, 163 – 172.

[2] H. Mikkers, M. Nawijn, J. Allen, C. Brouwers, E. Verhoeven, J. Jonkers, A. Berns, *Mol. Cell Biol*. **2004**, *24*, 6104 – 6115.

[3] J. D. Allen, E. Verhoeven, J. Domen, M. van der Valk, A. Berns, *Oncogene* **1997**, *15*, 1133 – 1141.

[4] H. Mikkers, M. Nawijn, J. Allen, C. Brouwers, E. Verhoeven, J. Jonkers, A. Berns, *Mol. Cell Biol*. **2004**, *24*, 6104 – 6115.

[5] R. Amson, F. Sigaux, S. Przedborski, G. Flandrin, D. Givol, A. Telerman, *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 8857 – 8861.

[6] R. Amaravadi, C. B. Thompson, *J. Clin. Invest*. **2005**, *115*, 2618 – 2624.

[7] D. Baytel, S. Shalom, I. Madgar, R. Weissenberg, J. Don, *Biochim. Biophys. Acta* **1998**, *1442*, 274 – 285.

[8] R. A. Davis, M. M. Simpson, R. B. Nugent, A. R. Carrol, V. M. Avery, T. Rali, H. Chen, B. Qurallo, R. J. Quinn, *J. Nat. Prod*. **2008**, *71*, 451 – 452.

[9] N. Ullah, K. M. Arafeh, *Tetrahedron Lett*. **2009**, *50*, 158 – 160.

[10] T. Sylvain, T. Thierry, G. Christian, I. Gilles, *Synth. Commun*. **2006**, *36*, 587 – 597.

[11] E. H. Matthew, L. S. Katherine, M. Motonori, R. B. James, K. G. David, S. S. Thomas, *J. Med. Chem*. **2006**, *49*, 1101 – 1112.