The First Total Synthesis of Galloyl Tyramine

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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 CH2Cl2 and Et3N 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 CH2Cl2 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 H2O, followed by the addition of LiOH.H2O (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 H2O (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]phenethyl-carbamate (7)

To a solution of acid 4 (0.3 g, 0.68 mmol) in THF (10 mL) was added SOCl₂ (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 CH₂Cl₂ (5 mL), and Et₃N (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 CH₂Cl₂. 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, CDCl₃): δ = 1.44 (s, 9 H, COOC(CH₃)₃), 2.81 (t, J = 7.4 Hz, 2 H, 2-H), 3.38 (m, 2 H, 1-H), 5.15 (s, 6 H, CH₂Ph), 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). – ¹³C NMR (125.7 MHz, CDCl₃): δ = 28.41 (COOC(CH₃)₃), 35.60
tert-Butyl 4-[3,4,5-tri(hydroxy)benzoyloxy]phenethyl-carbamate (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): \( \nu = 3382, 2966, 1701, 1685, 1318, 1190, 1164, 1033 \) cm\(^{-1}\). – 1H NMR (500 MHz, [D\(_6\)]DMSO): \( \delta = 1.44 \) (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, N-H COOC(CH\(_3\))\(_3\)), 7.15 (s, 2 H, 3'-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'). – 13CN M R (125.7 MHz, [D\(_6\)]DMSO): \( \delta = 28.28 \) (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', C-6'), 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\(_2\)Cl\(_2\) to produce 0.043 g (71 %) of 1. The spectral data of our synthetic 1 were identical to those of the natural material [8].