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Synthesis of a novel sphingosine kinase inhibitor (−)-F-12509A and determination of its absolute configuration

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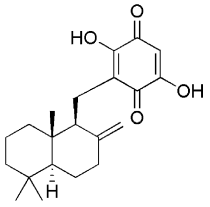
Abstract—The synthesis of a novel sphingosine kinase inhibitor, (−)-F-12509A ((−)-**1**), was achieved in a highly efficient manner that included nine longest linear steps and 45% overall yield from (−)-bicyclic β-ketoester (−)-**2**, and its absolute configuration was determined to be (5*S*,9*S*,10*S*).

As a novel sphingosine kinase (SphK) inhibitor, (−)-F-12509A ((−)-**1**), was isolated from a culture broth of a discomycete, *Trichopezizella barbata* SANK 25395, by Kohama and co-workers in 2000.[1,2] F-12509A is the first SphK inhibitor isolated from natural sources, and inhibits rat liver SphK in a dose-dependent manner with an IC_{50} value of 18 μM and in a competitive manner with respect to sphingosine (SPH).[1] This molecule showed no inhibitory activity toward other enzymes such as mammalian neutral sphingomyelinase, PI3-kinase, and protein kinase C (PKC) at 100 μM. These results indicated that F-12509A is a specific inhibitor of SphK, which catalyzes the phosphorylation of SPH at its primary hydroxy group to biosynthesize sphingosine1-phosphate (S1-P), and is known as a key enzyme that regulates the cellular S1-P level. S1-P has been paid much attention as a remarkable phospholipids based on the discovery of its biological receptor[3] in addition to its quite attractive biological activities such as cell division, cell growth, and platelet activation.[4] (−)-F-12509A ((−)-**1**) possesses a dihydroxybenzoquinone moiety attached to a drimane sesquiterpene skeleton. The unique dihydroxybenzoquinone moiety was found in some biologically interesting natural products such as maesaquinone.[5] However, only a few methods for preparation of this moiety have been reported in the literature.[5,6] Our interest in the sphingolipid chemistry, involving the design and synthesis of substrate analogs[7] and the synthesis of tool molecules useful for following sphingolipid metabolism,[8] prompted us to synthesize this novel and specific SphK inhibitor, (−)-F-12509A ((−)-**1**). We disclose herein the efficient synthesis of F-12509A and its dihydroderivative, along with determination of the absolute configuration of naturally occurring (−)-F-12509A ((−)-**1**) (see Fig. 1).

By searching the literature, we learned that hyatellaquinone is a mono-methyl ether of F-12509A and was synthesized from (−)- and (+)-arbicanal (**3**).[9] We then planned to follow the reported synthesis in order to construct the basic skeleton of F-12509A. According to our established procedure,[10] we easily synthesized (−)- and (+)-β-ketoester **2** by the resolution of enantiomers using an acetal formation with a chiral auxiliary, 1,4-*O*-dibenzyl-L-threitol (Scheme 1).

The Wittig olefination of (−)-**2** with triphenylphosphonium methylide followed by reduction and then



(-)-F-12509A ((-)-1)

Figure 1. Sphingosine kinase inhibitor (−)-F-12509A.

Keywords: Sphingosine kinase inhibitor; Dihydroxyquinone; Synthesis; Absolute configuration.
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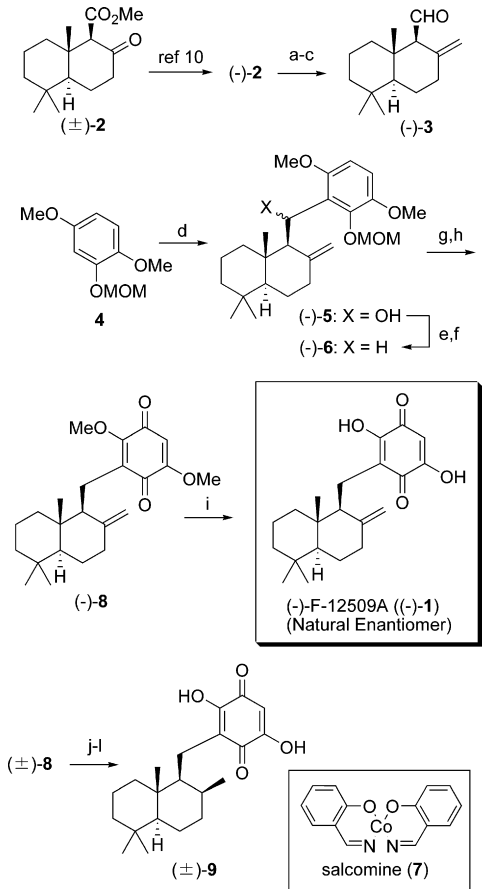

Scheme 1. Reagents and conditions: (a) $Ph_3P^+CH_3Br^-$, $NaNH_2$, THF, rt, 1 h; (b) $LiAlH_4$, THF, rt, 20 h (99%, two steps); (c) TPAP, NMO, CH_2Cl_2, rt, 30 min (100%); (d) *n*-BuLi, TMEDA, THF, rt, 1 h then (−)-**3**, rt, 5 min (94%); (e) (i) NaHMDS, THF, −78 °C, 30 min; (ii) CS_2, −60 °C, 1 h; (iii) MeI, 0 °C, 2 h; (f) *n*-Bu_3SnH, AIBN, C_6H_6, 80 °C, 2 h (92%, two steps); (g) 2 N HCl aq, AcOH, MeOH, rt, 24 h (100%); (h) salcomine (**7**), O_2, DMF, rt, 20 h (89%); (i) 4 N KOH aq, MeCN, reflux, 3 h (93%); (j) PtO_2, H_2, MeOH, rt, 8 h; (k) CAN, H_2O, MeCN, 0 °C, 20 min (100%, two steps); (l) 4 N KOH aq, MeCN, reflux, 15 h (89%).

oxidation, quantitatively produced (−)-arbicanal (**3**). Then, the aryllithium generated in situ by treatment of the benzenetriol derivative **4**, which was prepared from commercially available 2,5-dimethoxybenzaldehyde according to the reported procedure,[11] with *n*-BuLi in the presence of TMEDA was allowed to react with (−)-**3** to produce the corresponding alcohol (−)-**5** in good yield. The resulting hydroxyl group was removed using the Barton method via the xanthate ester[12] to provide (−)-**6** in 92% yield over two steps. The MOM group was removed by treatment with acid and the subsequent oxidation of the obtained phenol was achieved using salcomine (*N*,*N*-bis(salicylidene)ethylenediimino cobalt(II) (**7**) under an oxygen atmosphere[11] to successfully obtain *para*-quinone (−)-**8**[13] in 89% yield without the formation of its *ortho*-isomer. Finally, the two methoxy groups of **8** were replaced by 1,4-addition of a hydroxyl anion to dimethoxyquinone[6a] in acetonitrile to achieve the synthesis of (−)-F-12509A ((−)-**1**). The spectral and physical data of the synthesized compound[14] were in good agreement with those of the natural product including the optical rotation, $[\alpha]_D^{23}$ −95.2 (*c* 0.20, MeOH), (lit.[1] $[\alpha]_D^{25}$ −96 (*c* 0.25, MeOH)). Thus, the absolute configuration of the natural (−)-F-12509A ((−)-**1**) was confirmed as (5*S*,9*S*,10*S*) by the present synthesis. Using the same procedure, unnatural enantiomer (+)-**1** ($[\alpha]_D^{23}$ +92.8 (*c* 0.28, MeOH)) was also synthesized from bicyclic β-ketoester (+)-**2**. In addition, the dihydro analog (±)-**9** of F-12509A was synthesized from (±)-**8** by a sequence of hydrogenation of its *exo*-olefin, oxidation to the quinone, and replacement to the hydroxyl groups.[15]

Synthesized natural (−)-**1** and unnatural congener (+)-**1** showed almost the same inhibitory activity toward SphK, and moreover, both (±)-**1** and its dihydro analog (±)-**9** also showed inhibitory effects equal to natural (−)-**1** (IC_{50} values of four compounds were 17–19 μM). The detailed results of these biological activities will be reported elsewhere.

In summary, we achieved the total synthesis of the novel sphingosine kinase inhibitor, (−)-F-12509A ((−)-**1**), in an efficient manner (nine steps and 45% overall yield from bicyclic β-ketoester (−)-**2**), and determination of its absolute configuration as (5*S*,9*S*,10*S*). All the synthesized compounds such as (±)- and each enantiomer of F-12509A, and its dihydro analog (±)-**9**, showed an effective biological activity toward SphK.

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13. Data for (−)-**8**: $[\alpha]_D^{23}$ −67.6 (*c* 0.56, $CHCl_3$); IR (KBr, cm^{-1}) 2938, 2866, 1728, 1659, 1601, 1215, 1047, 849; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.69 (s, 1H), 4.68 (d, $J = 1.5$ Hz, 1H), 4.66 (d, $J = 1.5$ Hz, 1H), 4.06 (s, 3H), 3.78 (s, 3H), 2.69 (dd, $J = 13.6$, 10.7 Hz, 1H), 2.51 (dd, $J = 13.9$, 2.9 Hz, 1H), 2.29 (m, 1H), 1.90 (dt, $J = 13.4$, 2.9 Hz, 1H), 1.78 (br d, $J = 12.2$ Hz, 1H), 1.71 (m, 1H), 1.46–1.63 (m, 2H), 1.39 (m, 1H), 1.36 (m, 1H), 1.29 (m, 1H), 1.21 (m, 1H), 1.14 (dd, $J = 12.7$, 2.4 Hz, 2H), 0.86 (s, 3H), 0.81 (s, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.3, 182.8, 158.9, 156.0, 148.8, 130.9, 106.7, 105.3, 61.2, 56.3, 55.6, 55.0, 42.1, 40.2, 38.7, 38.4, 33.6, 33.6, 24.5, 21.7, 19.5, 19.2, 14.1; ESI HRMS *m/z* calcd for $C_{23}H_{32}O_4$ $[M+Na]^+$ 395.2198, found 395.2188.
14. Data for (−)-F-12509A ((−)-**1**): $[\alpha]_D^{23}$ −95.2 (*c* 0.20, MeOH), (lit.[1] $[\alpha]_D^{25}$ −96 (*c* 0.25, MeOH)); IR (KBr, cm^{-1}) 3322, 2928, 1640, 1616, 1352, 1318, 1190; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (br s, 2H), 5.98 (s, 1H), 4.67 (d, $J = 1.2$ Hz, 1H), 4.66 (d, $J = 1.2$ Hz, 1H), 2.66 (dd, $J = 14.2$, 11.0 Hz, 1H), 2.54 (dd, $J = 14.4$, 3.2 Hz, 1H), 2.40 (br d, $J = 11.5$ Hz, 1H), 2.32 (ddd, $J = 12.4$, 3.9, 2.4 Hz, 1H), 1.94 (dt, $J = 12.9$, 4.8 Hz, 1H), 1.79 (br dt, $J = 12.4$, 3.7 Hz, 1H), 1.72 (m, 1H), 1.50–1.68 (m, 2H), 1.41 (m, 1H), 1.35 (m, 1H), 1.32 (m, 1H), 1.25 (m, 1H), 1.17 (dd, $J = 12.7$, 2.7 Hz, 1H), 0.88 (s, 3H), 0.82 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.6, 116.9, 106.6, 102.0, 55.6, 54.1, 42.1, 40.1, 38.9, 33.6, 24.5, 21.7, 19.5, 18.8, 14.0; ESI HRMS *m/z* calcd for $C_{21}H_{28}O_4$ $[M-H]^-$ 343.1909, found 343.1901.
15. Data for (±)-**9**: IR (KBr, cm^{-1}) 3304, 2926, 2849, 1615, 1196, 829; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.99 (s, 1H), 2.53 (m, 2H), 1.88 (m, 1H), 1.81 (dt, $J = 12.0$, 3.2 Hz, 1H), 1.71 (m, 1H), 1.67 (m, 1H), 1.62 (ddt, $J = 13.6$, 13.6, 3.9 Hz, 1H), 1.61 (m, 1H), 1.53 (m, 1H), 1.42–1.52 (m, 2H), 1.38 (m, 1H), 1.30 (m, 1H), 1.20 (dd, $J = 12.6$, 4.1 Hz, 1H), 1.13 (m, 1H), 0.99 (d, $J = 7.3$ Hz, 3H), 0.93 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 127.0, 102.1, 56.8, 52.7, 39.3, 34.8, 33.4, 31.0, 30.7, 29.7, 21.6, 20.2, 18.5, 16.2, 15.9, 15.2; ESI HRMS *m/z* calcd for $C_{23}H_{34}O_4$ $[M+MeOH-H]^-$ 377.2328, found 377.2334.