Tetrahedron Letters 51 (2010) 2768–2770

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The first total synthesis of potent human chymase inhibitor SPF32629B via regioselective bromination and O-acylation strategy

Srinivasa Rao Vegi [a,b], Shanthaveerappa K. Boovanahalli [a,*], Balaram Patro [a,*], K. Mukkanti [b]

[a] Medicinal Chemistry Laboratory, GVK Biosciences Pvt. Ltd, Plot No. 28, IDA, Nacharam, Hyderabad 500 076, AP, India
[b] Chemistry Division, Institute of Science and Technology, JNT University, Kukatpally, Hyderabad 500 072, AP, India

ARTICLE INFO

Article history:
Received 20 February 2010
Revised 17 March 2010
Accepted 19 March 2010
Available online 25 March 2010

ABSTRACT

An efficient total synthesis of (±)-SPF32629B is described. The key features of the synthesis include regioselective bromination followed by carboxylation at C-3 and protecting-group-free regioselective acylation of hydroxyl group present at C7. Structure was determined by X-ray analysis.

SPF32629A and B (**1** and **2**, respectively, Fig. 1) make up a family of biologically interesting pyridone derivatives isolated from the cultured broth of *penicillium* sp. by Shimatani and Hosoya in 2004.[1] These compounds differ in structure only at C-3 and **2** is the carboxylated derivative of **1**. The preliminary biological evaluation revealed that both **1** and **2** demonstrated significant inhibitory activities against human chymase (IC_{50} = 0.25 and 0.42 μg/mL, respectively) and human elastase (IC_{50} = 4.9 and 4.5 μg/mL, respectively) and therefore expected to be useful for the treatment of inflammation-related various diseases and procoagulant.[1,2] Human chymase inhibitors are considered to be useful therapeutic agents in disorders such as congestive heart failure, allergy, vascular proliferation and chronic inflammation following fibrosis.[3] In this regard several chymase inhibitors have been reported in the literature.[4]

Thus, on account of their diverse structural features and their potential medicinal utility as human chymase inhibitors, **1** and **2** present themselves as important synthetic targets to explore their therapeutical potential. A systematic exploration of the properties, mechanism of action and biochemical significance of **1** and **2** requires efficient and versatile syntheses of these molecules. Besides, synthetic approaches to these molecules will also offer avenues to the discovery of more analogues with high selectivity and potent bioactivity than **1** and **2**. In this context, we have previously disclosed the first total synthesis of racemic **1**[5] and to the best of our knowledge so far no studies on the synthesis of **2** have been reported. Herein, we describe a concise and an efficient approach, designed to afford the first total synthesis of racemic **2**.

The retro-synthetic analysis of compound **2** is shown in Scheme 1. We envisioned the construction of **2** starting from **3** via regioselective bromination followed by insertion of carboxylic acid at C-3, coupled with tandem reduction and regioselective O-acylation at C7. While in turn **3** could be easily assembled starting from commercially available pyridine by following previously described protocols.[5,6]

As illustrated in Scheme 2, the total synthesis of (±)-SPF32629B commenced with known compound **3**, which can be efficiently prepared in five steps starting from cheaply available pyridine.[5,6]

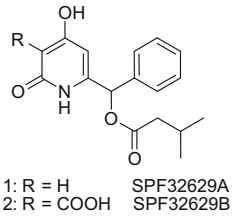
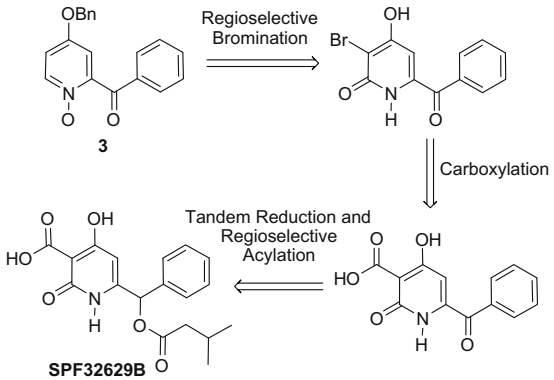


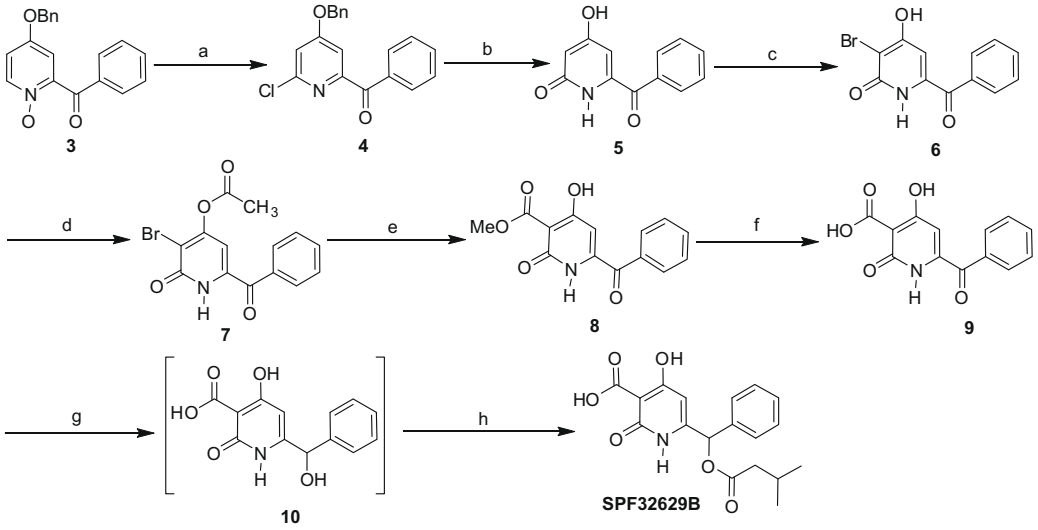
Figure 1. Structure of SPF32629A and B.



Scheme 1. Retrosynthetic analysis of SPF32629B.

* Corresponding authors. Tel.: +91 40 6451 3333x1163; fax: +91 40 2715 2999 (S.B.).
E-mail address: sveerappa.boovanahal@gvkbio.com (S.K. Boovanahalli).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.03.091

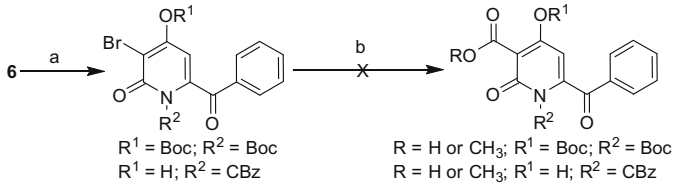


Scheme 2. Reagents and conditions: (a) $POCl_3$, reflux,12 h, 89%; (b) AcOH, H_2O, sealed tube, 180–190 °C, 12 h, 90%; (c) NBS, THF, DCM, −10 °C to 0 °C, 2 h, 97%; (d) Ac_2O, DMAP, rt, 5 h, 98%; (e) bis(benzonitrile)palladium(II) chloride, dppf, TEA, MeOH, CO, 300 psi, 120 °C, 3 h, 70%; (f) LiOH·H_2O, THF, H_2O, 50 °C, 36 h, quantitative (crude); (g) $NaBH_4$, THF, MeOH, 0 °C, 1 h, quantitative (crude); (h) isovaleric acid, EDC·HCl, DCM, THF, DMF, DMAP, rt, 12 h, 80% (over all yield for three steps).

Reaction of **3** with phosphorous oxychloride under reflux for 12 h yielded **4** in good yield. Compound **5** could be conveniently prepared by effecting debenzylation and dechlorination in a single step. Thus, when a solution of **4** in aqueous acetic acid was heated at 180–190 °C in a sealed tube for 12 h afforded **5** in high yield. Then, we examined direct conversion of **5** to **9** by insertion of carboxylic acid group regioselectively at C-3 under lithiation followed by carboxylation conditions (BuLi or LDA, then CO_2), however all attempts resulted in complex mixtures and failed to give the desired conversion. We therefore opted to install carboxylic acid group in a stepwise fashion through sequential bromination and palladium-catalyzed Heck carbonylation. Gratifyingly, when compound **5** was reacted with *N*-bromosuccinimide under optimized conditions afforded a highly regioselective bromination at C-3 to give **6** in excellent yield. The regioselective bromination at C-3 was confirmed by ^1H NMR, HMBC and COSY analysis. At this point, many attempts to introduce carboxyl group at C-3 in bromo-analogue **6** failed and hence, we thought to introduce protecting groups for amide and hydroxyl groups that would facilitate carbonylation. Accordingly, we examined various protecting groups including BOC, CBz, benzyl, TBDMS and acetyl protection. Although we could achieve Boc and CBz protection separately on **6**, the resulting protected compounds did not undergo subsequent carbonylation under various experimental conditions (Scheme 3).

On the other hand, all attempts to protect **6** with benzyl and TBDMS groups failed. Finally, to our delight, we found that the best results, in terms of protection and carbonylation were achieved through acetylation of **6**. Thus, acetylation of **6** rendered **7** in excellent yield and subsequently, after extensive experimentation, palladium-catalyzed esterification at C-3 of **7** was accomplished using bis(benzonitrile)palladium(II) chloride and dppf as palladium source in presence of TEA in methanol under 300 psi CO pressure to afford **8**. This procedure allowed a remarkably facile incorporation of methyl ester moiety at C-3 in conjunction with regeneration of free hydroxyl group at C-4. Further hydrolysis of **8** with lithium hydroxide monohydrate furnished the requisite acid derivative **9** in good yield.

Having efficiently synthesized the appropriately substituted pyridone core **9**, we turned our attention toward construction of final target molecule. Based on the poor selectivity of benzylation or TBDMS protection of OH and CONH groups of **5** and poor stability of acetyl group in **7**; we hypothesized that **2** could be regioselectively assembled in a one-pot procedure by a tandem reduction and acylation protocol in presence of free OH, COOH and CONH groups. Accordingly, reduction of **9** under standard sodium borohydride mediated reduction conditions furnished the requisite crude alcohol **10** in quantitative yield, which upon extractive isolation was acylated without further purification. Gratifyingly, as expected the resulting crude alcohol **10** underwent coupling with isovaleric acid in a regioselective manner to produce SPF32629B in good yield with high purity. The spectral data including IR,



Scheme 3. Reagents and conditions: (a) Boc anhydride, DCM, TEA, 0 °C to rt, 6 h, 90% or CBzCl, TEA, DCM, 0 °C to rt, 3 h; (b) bis(benzonitrile)palladium(II) chloride, dppf TEA, MeOH, CO, 300 psi, 120 °C, 12 h or BuLi, THF, −78 °C, 1 h, then CO_2.

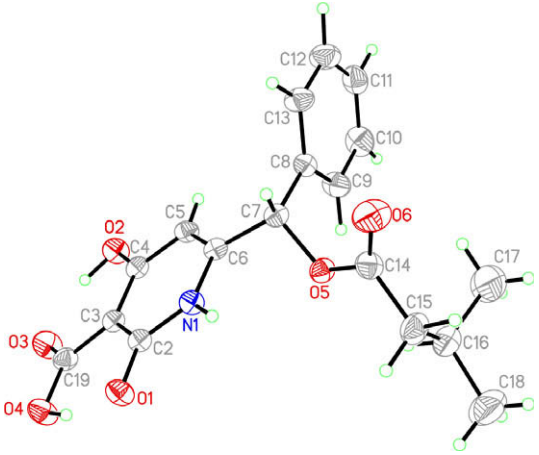


Figure 2. ORTEP diagram of **2** showing the crystal structure.

MASS, ^{1}H NMR, ^{13}C NMR and LC–MS of our synthetic compound **2** were in consistent with the reported data.[1,2,7] The assigned structure was also firmly established by single-crystal X-ray analysis as shown in Figure 2.[8] With this, the total synthesis of **2** was completed in an overall yield of 43% and this constitutes the first reported total synthesis of (±)-SPF32629B.

In conclusion, we have described a highly efficient synthesis of SPF32629B, featuring sequential regioselective carboxylation at C-3 followed by late-stage in situ C7-keto reduction and regioselective O-acylation. Studies on the enantioselective synthesis including biological activities of SPF32629B and their analogues are currently in progress and will be reported in due course.

Acknowledgments

We thank Management, GVK Biosciences Private Limited for the financial support and encouragement. Help from the analytical department for the analytical data is appreciated. We thank Dr. Raghavaiah Pallepogu for the single-crystal X-ray analysis data.

References and notes

1. Shimatani, T.; Hosoya, Y. Japanese Patent JP 2004067584, 2004; *Chem. Abstr.* **2004**, *140*, 216278.
2. Shimatani, T.; Hosotani, N.; Ohnishi, M.; Kumagai, K.; Saji, I. *J. Antibiot.* **2006**, *59*, 29–34.
3. (a) Muto, T.; Fukami, H. *IDrugs* **2002**, *5*, 1141–1150; (b) Akahoshi, F. *Drugs Future* **2002**, *27*, 765–770; (c) Doggrell, S. A.; Wanstall, J. C. *Expert Opin. Investig. Drugs* **2003**, *12*, 1429–1432; (d) Fukami, H.; Okunishi, H.; Miyazaki, M. *Curr. Pharm. Des.* **1998**, *4*, 439–453; (e) Tomimori, Y.; Muto, T.; Fukami, H.; Saito, K.; Horikawa, C.; Tsuruoka, N.; Saito, M.; Sugiura, N.; Yamashiro, K.; Sumida, M.; Kakutani, S.; Fukuda, Y. *Lab. Invest.* **2002**, *82*, 789–794; (f) Watanabe, N.; Tomimori, Y.; Saito, K.; Miura, K.; Wada, A.; Tsudzuki, M.; Fukuda, Y. *Int. Arch. Allergy Immunol.* **2002**, *128*, 229–234; (g) Kokkonen, J. O.; Lindstedt, K. A.; Kovanen, P. T. *Circulation* **2003**, *107*, 2522–2524; (h) Matsumoto, T.; Wada, A.; Tsutamoto, T.; Ohnishi, M.; Isono, T.; Kinoshita, M. *Circulation* **2003**, *107*, 2555–2558; (i) Kanemitsu, H.; Takai, S.; Tsuneyoshi, H.; Nishina, T.; Yoshikawa, K.; Miyazaki, M.; Ikeda, T.; Komeda, M. *Hypertens. Res.* **2006**, *29*, 57–64; (j) Tomimori, Y.; Muto, T.; Saito, K.; Tanaka, T.; Maruoka, H.; Sumida, M.; Fukami, H.; Fukuda, Y. *Eur. J. Pharmacol.* **2003**, *478*, 179–185; (k) Sakaguchi, M.; Takai, S.; Jin, D.; Okamoto, Y.; Muramatsu, M.; Kim, S.; Miyazaki, M. *Eur. J. Pharmacol.* **2004**, *493*, 173–176; (l) Takai, S.; Jin, D.; Muramatsu, M.; Okamoto, Y.; Miyazaki, M. *Eur. J. Pharmacol.* **2004**, *501*, 1–8; (m) Aoyama, Y. *Expert Opin. Ther. Patents* **2001**, *11*, 1423–1428.
4. (a) Akahoshi, F. *Curr. Pharm. Des.* **2003**, *9*, 1191–1199; (b) Akahoshi, F.; Ashimori, A.; Sakashita, H.; Yoshimura, T.; Imada, T.; Nakajima, M.; Mitsutomi, N.; Kuwahara, S.; Ohtsuka, T.; Fukaya, C.; Miyazaki, M.; Nakamura, N. *J. Med. Chem.* **2001**, *44*, 1286–1296; (c) Akahoshi, F.; Ashimori, A.; Sakashita, H.; Yoshimura, T.; Eda, M.; Imada, T.; Nakajima, M.; Mitsutomi, N.; Kuwahara, S.; Ohtsuka, T.; Fukaya, C.; Miyazaki, M.; Nakamura, N. *J. Med. Chem.* **2001**, *44*, 1297–1304; (d) Masaki, H.; Mizuno, Y.; Tatui, A.; Murakami, A.; Koide, Y.; Satoh, S.; Takahashi, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4085–4088; (e) Tanaka, T.; Muto, T.; Maruoka, H.; Imajo, S.; Fukami, H.; Tomimori, Y.; Fukuda, Y.; Nakatsuka, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3431–3434; (f) Iijima, K.; Katada, J.; Hayashi, Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 413–418; (g) Koide, Y.; Tatsui, A.; Hasegawa, T.; Murakami, A.; Satoh, S.; Yamada, H.; Kazayama, S.-I.; Takahashi, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 25–29; (h) Groutas, W. C.; Schechter, N. M.; He, S.; Yu, H.; Huang, P.; Tu *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2199–2204.
5. Vegi, S. R.; Boovanahalli, S. K.; Sharma, A. P.; Mukkanti, K. *Tetrahedron Lett.* **2008**, *49*, 6297–6299.
6. Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534–551.
7. *Spectral data of* (±)-SPF32629B: R_f = 0.3 (5% methanol/dichloromethane); mp 129–132 °C; IR (KBr pellet): ν_{max} 3461, 1742, 1688, 1639 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$)) δ 14.24 (1H, br s, D_2O exchangeable COOH), 13.51 (1H, br s, D_2O exchangeable OH), 10.1 (1H, br s, D_2O exchangeable CONH), 7.42–7.34 (5H, m), 6.63 (1H, s), 6.22 (1H, s), 2.34 (2H, d, J = 7.2 Hz), 2.15–2.09 (1H, m), 0.94 (6H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.94 (C), 171.83 (C), 171.35 (C), 165.93 (C), 151.07 (C), 134.75 (C), 129.82 (CH), 129.34 (2CH), 127.21 (2CH) 101.35 (CH), 96.84 (C), 72.67 (CH); 42.95 (CH_2); 25.69 (CH); 22.28 (CH_3); 22.26 (CH_3); MS (ESI) m/z 344.20 $(M-H)^-$; LC–MS (ES) m/z calcd for $C_{18}H_{18}NO_6$ $[M-H]^-$: 344.36, found: 344.2; Develosil ODS MG-3 (4.6 × 33 mm), mobile phase: A: 0.1% aq HCOOH, B: 0.1% HCOOH (acetonitrile/methanol (50:50)), T/%B: 0/30, 4/90, 10/90, 10.1/30; flow rate: 1 mL/min, diluent: acetonitrile; UV: 301 nm, t_R = 4.61, purity = 98.72%; HPLC—column used: Eclipse XDB-C18 (4.6 × 150 mm) 5 μ, mobile phase: A: 0.1 M formic acid; B: methanol; T/%B: 0/50, 8/90, 15/90, 15.1/50; flow rate: 1.0 mL/min, diluent: (A/ACN, 1:1); UV: 303 nm; t_R = 9.13; purity = 99.12%. Chiral HPLC—column used: Chiral PAK-AD-H (4.6 × 250 mm), 5 μ, mobile phase: A: 0.1% TFA in *n*-hexanes, B: ethanol (70:30), isocratic; flow rate: 0.7 mL/min, diluent: ethanol, run time: 25 min, UV: 304 nm, t_R = 8.69 and 12.57.
8. *Crystal data for* (±)-SPF32629B: $C_{18}H_{19}NO_6$; M = 345.34, temperature = 293(2) K, wavelength = 0.71073 Å, crystal system, space group = triclinic, P, unit cell dimensions a = 5.4767(8) A α = 70.750(15) °. b = 11.6443(18) A β = 83.818(13) °, c = 14.733(3) A γ = 88.399(13) °. Volume = 881.8(2) $Å^3$, Z, calculated density = 2, 1.301 Mg/m^3, absorption coefficient = 0.098 mm^{-1}, $F(000)$ = 364, crystal size = 0.42 × 0.20 × 0.18 mm, θ range for data collection = 3.51–24.71 °, limiting indices = $-6 \leq h \leq 5$, $-13 \leq k \leq 10$, $-16 \leq l \leq 17$, reflections collected/unique = 4399/2902 [R(int) = 0.0270], completeness to θ = 24.71 96.3%, max. and min. transmission = 0.9825 and 0.9599, refinement method = full-matrix least-squares on F^2, data/restraints/parameters = 2902/0/281, goodness-of-fit on F^2 = 0.908, final R indices [$I > 2\sigma(I)$] R_1 = 0.0466, wR_2 = 0.1092, R indices (all data) R_1 = 0.0908, wR_2 = 0.1228, extinction coefficient = 0.004(4), largest diff. peak and hole = 0.169 and −0.176 e $Å^3$. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC Deposition No. 759752).