

A New Enantioselective Total Synthesis of AI-77-B

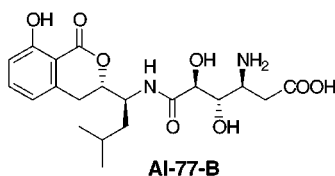
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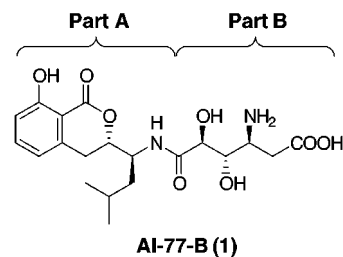
ABSTRACT



An enantioselective total synthesis of AI-77-B (**1**), a gastroprotective substance isolated from a culture broth of *Bacillus pumilus* AI-77, was performed in high overall yield. In this synthesis, the dihydroisocoumarin part **14** and the dihydroxyamino acid part **20** were both assembled from D-ribose as the common chiral source. For the construction of **14** a bromobenzofuran derivative was used as a novel salicylic acid synthon. Finally, DEPC-mediated condensation of **14** and **20** yielded AI-77-B (**1**).

The AI-77s are a group of 3,4-dihydroisocoumarin antibiotics that have been isolated from a culture broth of *Bacillus pumilus* AI-77.^{1,2} The major component, AI-77-B (**1**), has been found to exhibit potent gastroprotective activity without anticholinergic, antihistaminergic, or central suppressive effects.³ Due to its unique structure and its characteristic biological activity, AI-77-B (**1**) has attracted a great deal of attention from synthetic chemists. To date, four syntheses of this compound have been reported by Hamada/Shioiri,⁴ Thomas,⁵ Procter,⁶ and Vogel.⁷ Several approaches to the partial synthesis of **1** have also been reported.⁸

Our own enantioselective synthesis of **1** uses two segments, the dihydroisocoumarin (part A) and the dihydroxyamino acid (part B), which were both assembled from D-ribose as the common chiral source.⁹ To construct part A,



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compound **14**, our earlier approach relied on novel carbon–carbon bond-forming reactions¹⁰ of triflate **9** with an aryl Grignard reagent and subsequent regioselective metalation/

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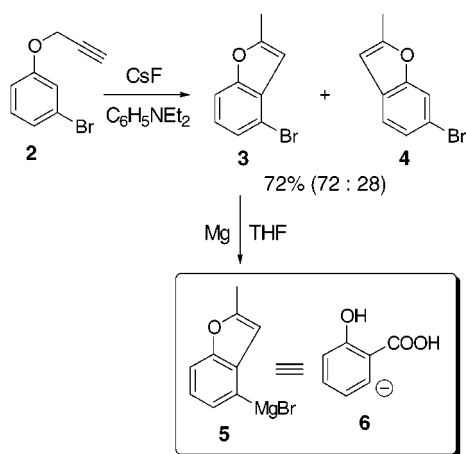
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carboxylation.^{9a} However, the latter step did not prepare enough of the product, and we elected to adopt a completely different strategy using benzofuran **5** for the Grignard partner as a novel salicylic acid synthon, such as **6**. The requisite **5** was prepared by CsF-mediated rearrangement¹¹ of *m*-bromophenyl propargyl ether (**2**) in good regioselectivity (Scheme 1). Since **3** and **4** were inseparable at this stage,¹² the corresponding Grignard reagent was prepared as a mixture.

Scheme 1



An efficient copper-catalyzed coupling reaction of the triflate **9** derived from **7**¹³ with the Grignard reagent **5** was achieved at room temperature to afford **10** in 93% yield (Scheme 2). Ozonolysis of **10** followed by hydrolysis of the resulting acetate gave the salicylaldehyde **11** (82.7% for two steps).¹⁴ At this stage, it became possible to chromatographically separate **11** from its regioisomer originating from **4**.

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(12) These isomers could be separated by JAI Recycling Preparative HPLC LC-908, and each structure was determined unambiguously by ¹H NMR (400 MHz): **3**: δ 2.46 (3H, s), 6.42 (1H, t, *J* = 1.0 Hz), 7.06 (1H, t, *J* = 8.1 Hz), 7.32, 7.34 (each 1H, dd, *J* = 8.1, 1.0 Hz). **4**: δ 2.42 (3H, s), 6.32 (1H, d, *J* = 0.7 Hz), 7.28 (1H, ddd, *J* = 8.3, 1.4, 0.7 Hz), 7.30 (1H, d, *J* = 8.3 Hz), 7.55 (1H, dd, *J* = 1.4, 0.7 Hz).

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Conversion of **11** to **14** was straightforward.^{9a} Thus, protection of **11** as its benzyl ether followed by deprotection of an acetonide function gave a diol (present as a form of hemiacetal), which was further oxidized with NaClO₂/NaHSO₃/30% H₂O₂ under carefully controlled conditions¹⁵ to afford hydroxylactone **12**. Compound **12** was then transformed to **14**, [α]_D²² = −55.4° (*c* 1.01, MeOH) (lit.^{6b} [α]_D = −55.6° (*c* 1.08, MeOH)) and mp 203–205 °C (lit.^{6b} mp 209–212 °C), via azidation with S_N2 inversion and catalytic hydrogenation (three steps, 96% overall yield).

As illustrated in Scheme 3, the optically pure **20** (part B) was also assembled from D-ribose.^{9c} Treatment of **15**¹⁷ with *p*-methoxybenzylamine followed by acetylation gave lactam **16**. Stereoselective alkylation of **16** with allyltrimethylsilane by the assistance of BF₃·OEt₂ proceeded quantitatively to afford **17** via a well-known *N*-acylpyrrolidinium ion intermediate.¹⁸ Deprotection of the PMB group in **17** by CAN-oxidation produced **18** (57%) along with its *p*-methoxybenzoyl derivative (38%); the latter compound could be hydrolyzed smoothly to **18** under basic conditions, and hence **18** was obtained in an overall yield of 85%. Reprotection of **18** with Boc₂O/cat. DMAP gave the *N*-Boc lactam **19**, [α]_D²⁵ = +89.5° (*c* 0.98, CHCl₃) and mp 65.5–67 °C, quantitatively.

The final steps of our AI-77-B (**1**) synthesis are shown in Scheme 4. Since our initial attempts to realize the uncatalyzed condensation of **14** with **19** at high pressure were all unsuccessful due to the undesired isomerization of **14**,^{9b,c,19} we applied Hamada's conditions.⁴ Accordingly, DEPC-mediated condensation of **14** with **20** at 0 °C (DMF, Et₃N, 12 h) was achieved in 77% yield.¹⁹ In situ generation of acid **20** from **19** and also gradual addition of Et₃N were essential to increase the yield of this step. Oxidative cleavage of the terminal double bond with RuCl₃ and NaIO₄²⁰ followed by deprotection of an acetonide as well as an *N*-Boc function under mildly acidic conditions (3% HCl in MeOH) yielded AI-77-B (**1**) (two steps, 85% overall yield), [α]_D²³ = −76.1° (*c* 0.09, MeOH) (lit.^{4b} [α]_D²² = −78.2° (*c* 0.08, MeOH)) and mp 147.5–148.0 °C (lit.^{1c} mp 139.5–140.0 °C). The

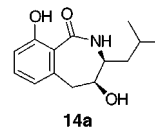
(15) NaClO₂ oxidation was best achieved by using H₂O₂ as the HOCl scavenger.¹⁶ When the oxidation was performed in the absence of H₂O₂, **12** was obtained in only 50% yield, along with 48% of the aromatic chlorinated compounds.

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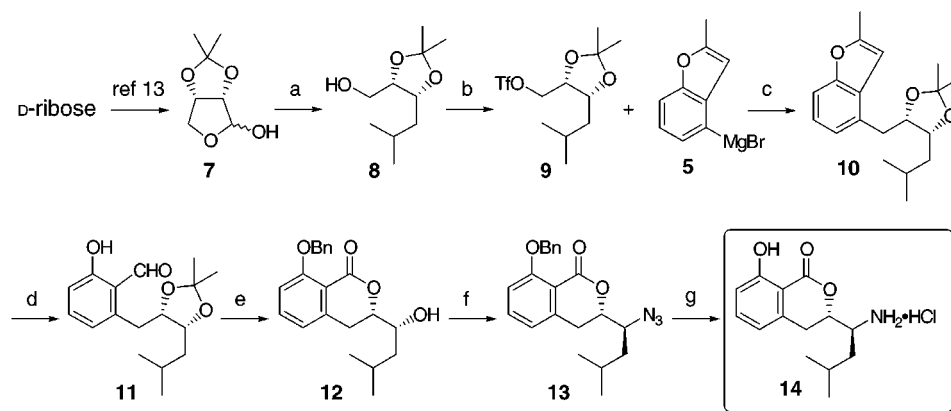
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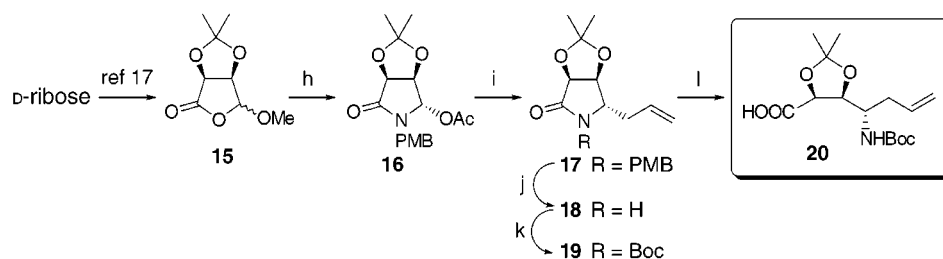
(19) As mentioned by Shimojima et al.,^{1c} the free amine of **14** was readily isomerized to the corresponding seven-membered lactam **14a**. This tendency significantly decreased the product yield when the condensation of **14** with **20** was conducted at room temperature.



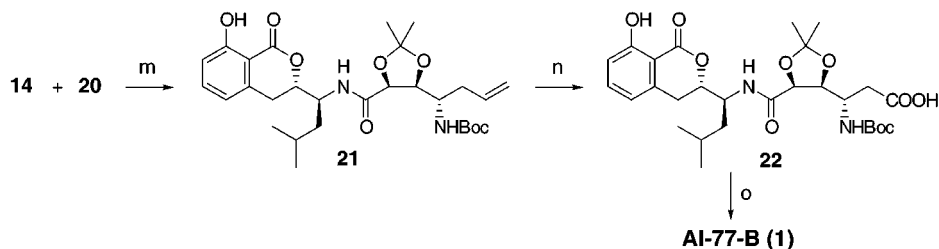
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Scheme 2^a

^a Legend: (a) (i) $(\text{CH}_3)_2\text{C}=\text{PPh}_3$, THF, -30°C to room temperature, 96%, (ii) H_2 , 10% Pd/C, K_2CO_3 , AcOEt, quantitative; (b) Tf_2O , pyridine, CH_2Cl_2 , -15°C , quantitative; (c) CuBr (0.3 equiv), THF, 0°C to room temperature, 12 h, 93%; (d) (i) O_3 , CH_2Cl_2 , -78°C , then Me_2S , 88%, (ii) aqueous K_2CO_3 , MeOH, 94%; (e) (i) BnBr, K_2CO_3 , acetone, reflux, 94%, (ii) 60% HClO_4 (cat.), aqueous CH_3CN , 0°C , 96%, (iii) NaClO_2 , NaHSO_3 , 30% H_2O_2 , KH_2PO_4 , aqueous CH_3CN , 95%; (f) (i) MsCl , Et_3N , CH_2Cl_2 , (ii) NaN_3 (10 equiv), 18-crown-6, DMF, 80°C , 22 h, 98% in two steps; (g) H_2 , 10% Pd(OH)₂/C, 3% HCl in MeOH, 98%.

Scheme 3^a

^a Legend: (h) 4-MeOC₆H₄CH₂NH₂, EtOH, 0°C , 1 h, then Ac_2O , pyridine, DMAP, quantitative; (i) $\text{CH}_2=\text{CHCH}_2\text{SiMe}_3$, $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , 0°C to room temperature, quantitative; (j) (i) CAN, aqueous CH_3CN , 0°C , (ii) 0.23 M KOH, THF/ H_2O (5:4), room temperature, overall 85%; (k) Boc_2O , cat. DMAP, THF, room temperature, quantitative; (l) 1.0 M LiOH, aqueous THF.

Scheme 4^a

^a Legend: (m) DEPC, Et_3N , DMF, 0°C , 12 h, 77%; (n) RuCl_3 , NaIO_4 , $\text{CCl}_4/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (2:2:3), room temperature, 3 h; (o) (i) 3% HCl in MeOH, 11 h, (ii) 0.1 M NaOH (pH 9), 3 h, (iii) 0.1 M HCl (pH 6.5), 85% from **21**.

spectroscopic data of the synthesized product were identical in all respects with those provided for the natural substance.²¹

In conclusion, an efficient, enantioselective total synthesis of AI-77-B (**1**) has been accomplished using a 12-step

(21) Our synthetic **1** was consistent with the published data.^{1c} We also thank Professor Y. Hamada (Chiba University) for providing proton and carbon NMR spectra of authentic **1**.

sequence from chiral triflate **9**, with an overall yield of 41.5%. The average yield per step is 93%, and this constitutes the most efficient synthesis to date. In addition, this route provides a new rapid entry to an 8-hydroxydihydroisocoumarin framework using bromobenzofuran **3** as the salicylic acid synthon. This may be useful for deriving a wide variety of dihydroisocoumarin families of natural products.

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Supporting Information Available: Text giving experimental procedures and figures giving NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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