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A New Enantioselective Total Synthesis of AI-77-B

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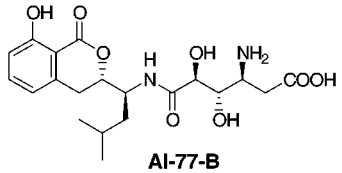
ABSTRACT

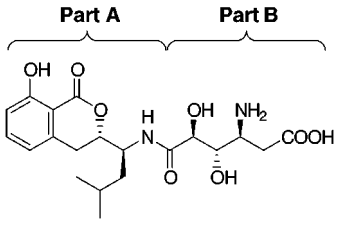


AI-77-B

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,



AI-77-B (1)

compound **14**, our earlier approach relied on novel carbon−carbon bond-forming reactions[10] of triflate **9** with an aryl Grignard reagent and subsequent regioselective metalation/

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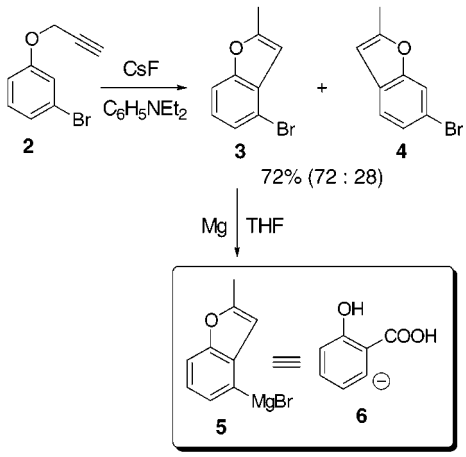
carboxylation.[9a] However, the latter step did not prepare enough of the product, and we elected to adopt a completely different strategy using benzofuran **5** for the Grignard partner as a novel salicylic acid synthon, such as **6**. The requisite **5** was prepared by CsF-mediated rearrangement[11] 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**. 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 $NaClO_2$/$NaHSO_3$/30% H_2O_2 under carefully controlled conditions[15] to afford hydroxylactone **12**. Compound **12** was then transformed to **14**, $[\alpha]^{22}_D = -55.4°$ (*c* 1.01, MeOH) (lit.[6b] $[\alpha]_D = -55.6°$ (*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 $BF_3{\cdot}OEt_2$ 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 Boc_2O/cat. DMAP gave the *N*-Boc lactam **19**, $[\alpha]^{25}_D = +89.5°$ (*c* 0.98, $CHCl_3$) 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, Et_3N, 12 h) was achieved in 77% yield.[19] In situ generation of acid **20** from **19** and also gradual addition of Et_3N were essential to increase the yield of this step. Oxidative cleavage of the terminal double bond with $RuCl_3$ and $NaIO_4$[20] 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), $[\alpha]^{23}_D = -76.1°$ (*c* 0.09, MeOH) (lit.[4b] $[\alpha]^{22}_D = -78.2°$ (*c* 0.08, MeOH)) and mp 147.5−148.0 °C (lit.[1c] mp 139.5−140.0 °C). The

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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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(15) $NaClO_2$ oxidation was best achieved by using H_2O_2 as the HOCl scavenger.[16] When the oxidation was performed in the absence of H_2O_2, **12** was obtained in only 50% yield, along with 48% of the aromatic chlorinated compounds.

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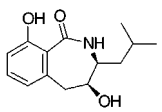
(19) As mentioned by Shimojima et al.,[1c] the free amine of **14** was readily isomerized to the corresponding seven-membered lactam **14a**. This tendency significantly decreased the product yield when the condensation of **14** with **20** was conducted *at room temperature*.



14a

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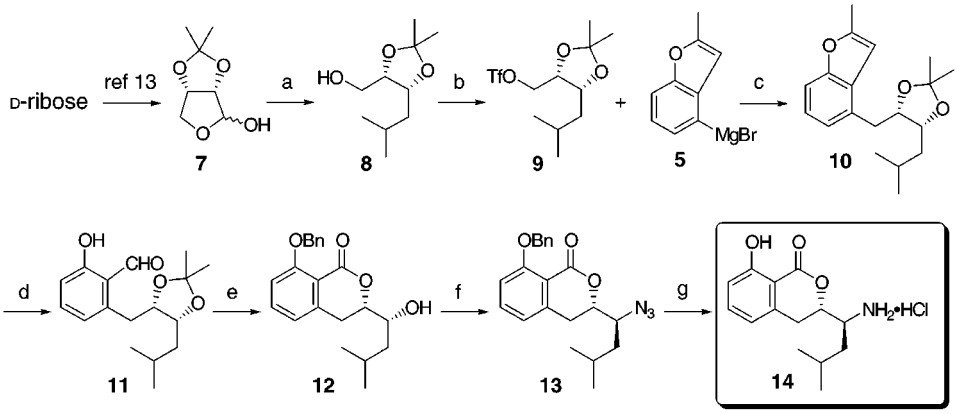
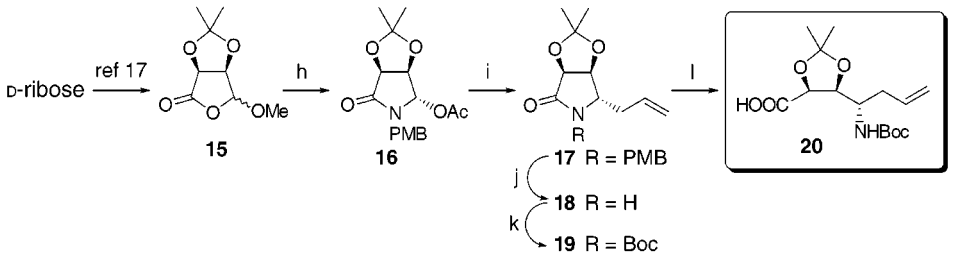
Scheme 2[a]



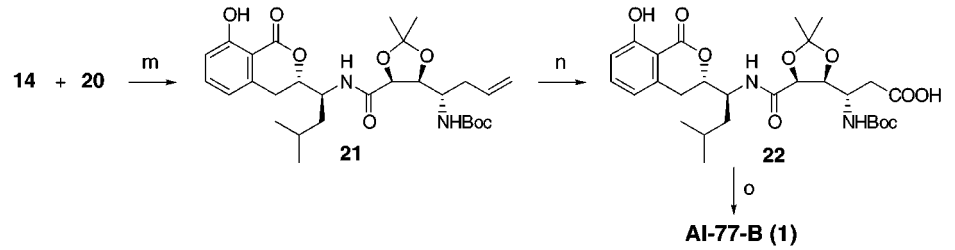
[a] Legend: (a) (i) $(CH_3)_2C{=}PPh_3$, THF, −30 °C to room temperature, 96%, (ii) H_2, 10% Pd/C, K_2CO_3, AcOEt, quantitative; (b) Tf_2O, pyridine, CH_2Cl_2, −15 °C, quantitative; (c) CuBr (0.3 equiv), THF, 0 °C to room temperature, 12 h, 93%; (d) (i) O_3, CH_2Cl_2, −78 °C, then Me_2S, 88%, (ii) aqueous 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-$MeOC_6H_4CH_2NH_2$, EtOH, 0 °C, 1 h, then Ac_2O, pyridine, DMAP, quantitative; (i) $CH_2{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, 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) $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$ (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 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.

(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**.

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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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