yield upon the addition of solvent may be due to the reduced pressures from cavity implosion caused by solvent vapor present in the cavities.

In summary, ultrasonication can be a simple, effective method to promote cycloadditions, possibly a substitute for high-pressure conditions. Furthermore, **1** has proven a useful dienophile for the synthesis of several biologically active abietanoid natural products. Thus the reaction of **8** with **1** directly gave **2** (76%, 10:3).[11] Nortanshinone (**3**) was similarly produced from the cycloadduct of **9** and **1** (65%, 8:1) following deprotection by passage through a column of silica gel impregnated with $FeCl_3$.[12] Synthetic compounds (**2**, **3**, and **4**) were identical with authentic samples.[3c,13]

Acknowledgment. We thank the Camille and Henry Dreyfus Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corp., and the National Institutes of Health (Grant GM-38014) for support. We also thank Professor Hou Wei Luo of the Nanjing College of Pharmacy for providing authentic samples of **2**, **3**, **4**, and **22** and Francis J. Hannon for assistance in running the high-pressure reactions.

(10) The ratio of cycloadduct regioisomers reported in ref 4 for diene **6** was inadvertantly reversed.

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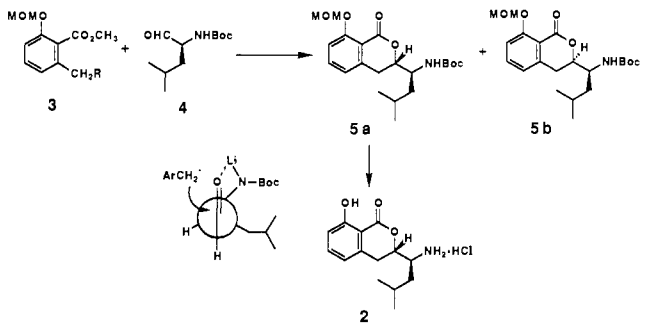
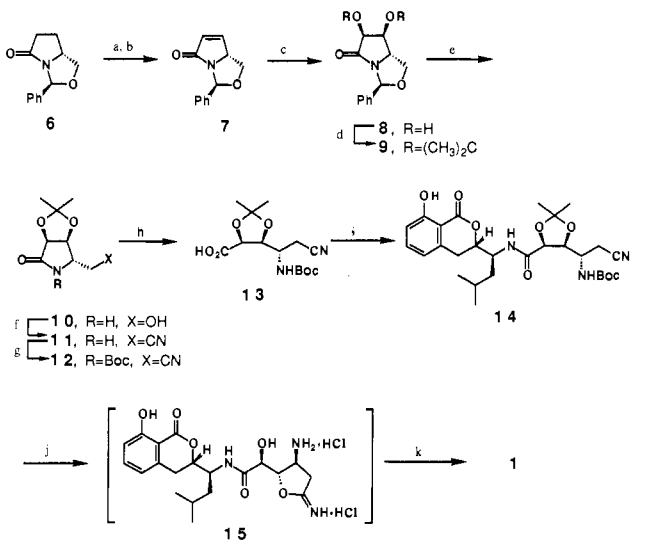
Scheme I



Scheme II[a]



[a] Reagents and conditions: (a) 1.3 equiv of LDA, THF, −70 °C, 0.5 h; then 1.2 equiv of PhSeBr (prepared in situ from Ph_2Se_2 and Br_2), THF, −70 °C, 15 min; (b) ozone, CH_2Cl_2, −74 °C, 2 h; pyridine, −74 °C → room temperature, 75% from **6**; (c) 0.1 equiv of OsO_4, 1.4 equiv of NMO, aqueous acetone, room temperature, 15 h, 65%; (d) an excess of 2,2-dimethoxypropane, PPTS (cat.), acetone, room temperature, 10 h, 98%; (e) 5% Pd–C, NH_2NH_2·H_2O, MeOH, 95%; (f) 2 equiv of KCN, 0.1 equiv of 18-crown-6, 1.1 equiv of Bu_3P, 1.1 equiv of CCl_4, CH_3CN, 30–40 °C, 1 h; then 70–80 °C, 2 h, 71%; (g) 1.15 equiv of $(Boc)_2O$, DMAP (cat.), CH_3CN, room temperature, 1 h, 92%; (h) LiOH, 70% aqueous THF, room temperature, 30 min, 70%; (i) **2**, 1.25 equiv of DEPC, 3.2 equiv of Et_3N, DMF, 0 °C, 3 h, room temperature, 20 h; then an additional 0.45 equiv of DEPC, room temperature; an additional 1.47 equiv of Et_3N, room temperature, 11 h, 70%; (j) an excess of trimethyl orthoformate, 5% HCl–MeOH, 5 °C, 44.5 h; (k) H_2O, 12 h; 0.1 N NaOH (pH 9), aqueous MeOH, room temperature, 3 h; 0.1 N HCl (pH 6.5), 76% from **14**.

Stereoselective Total Synthesis of AI-77-B, a Gastroprotective Substance from *Bacillus pumilus* AI-77[1,2]

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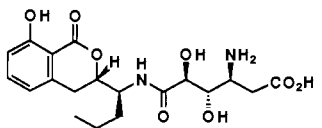
Received October 11, 1988

AI-77-B (**1**),[3] isolated from a culture broth of *Bacillus pumilus* AI-77 as the major product with characteristic fluorescence, is a unique naturally occurring 3,4-dihydroisocoumarin derivative having a hydroxy amino acid side chain.[4] Its absolute stereostructure containing *S* configurations at all five chiral centers has been established by Shimojima and co-workers[3] through X-ray analysis in combination with chemical and spectral studies. AI-77-B has been found to exhibit potent antiulcerogenicity action without central suppressive, anticholinergic, and antihistaminergic properties.[3b,5] We wish to report the first synthesis of AI-77-B (**1**) in a stereoselective and convergent manner, which provides an easy access to many other congeners required for pharmacological evaluation.[6]



1 (AI-77-B)

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(6) Since AI-77-B has been transformed to AI-77-C, -D, and -F,[3a,c] this synthesis constitutes a formal synthesis of these congeners.

0002-7863/89/1511-1524$01.50/0

Construction of the dihydroisocoumarin derivative **2**, the western fragment of **1**, commenced with transformation of ethyl 6-methylsalicylate[7] to the methoxymethyl (MOM) methyl ester **3** (R = H) in the usual manner. Reaction of (*tert*-butyloxycarbonyl (Boc))-L-leucinal (**4**)[8] with the in situ generated benzylic anion **3** (R = Li), prepared by treatment with lithium diisopropylamide (LDA) in the presence of tetramethylethylenediamine in THF (−78 °C, 1 h), afforded a separable mixture of **5a** and **5b** in 32% yield (61% conversion yield). By use of an excess of LDA (2.6 equiv) and **4** (1.4 equiv), the desired **5a** was obtained as the major product with 81:19 diastereoselectivity.[9] The diastereoselection in this reaction can be explained in terms of Cram's chelation control as shown in Scheme I. The stereochemistry of **5a** was firmly established by its conversion to **2** (mp 206-207 °C, $[\alpha]^{22}_D$ −47.4° (*c* 0.11, MeOH)), which was completely identical with the sample (mp 210 °C, $[\alpha]^{22}_D$ −47.45° (*c* 0.11, MeOH)) derived from natural Al-77-B.[3]

Construction of the hydroxy amino acid moiety **13**, the eastern building block of **1**,[10] started from the *N,O*-benzylidene derivative **6** of D-pyroglutaminol, prepared from D-glutamic acid by the known procedure.[11] Treatment of **6** with LDA in THF followed by phenylselenyl bromide afforded the crude selenide, which was oxidized with ozone in methylene chloride to give the α,β-unsaturated lactam **7** (mp 85-86 °C, $[\alpha]^{26}_D$ −215.6° (*c* 1.05, $CHCl_3$)) in 75% yield. Catalytic osmylation of **7** in aqueous acetone in the presence of *N*-methylmorpholine *N*-oxide (NMO) stereoselectively proceeded on the less hindered convex side with 98.4:1.6 diastereoselectivity, giving after chromatographic purification the desired β-diol **8** (mp 164-166 °C, $[\alpha]^{25}_D$ −221° (*c* 1.14, MeOH)) in 65% yield. After protection of the diol group as the acetal, removal of the benzylidene function of the acetonide **9** was achieved under catalytic hydrogen-transfer conditions using palladium-carbon and hydrazine hydrate in MeOH,[12] providing the lactam alcohol **10** (mp 141-142 °C, $[\alpha]^{24}_D$ +46.7° (*c* 1.03, MeOH)) in 95% yield. Introduction of the C_1 unit to **10** was accomplished by our own method[13] using potassium cyanide, 18-crown-6, tributylphosphine, and carbon tetrachloride to give the nitrile **11** (mp 207-208 °C, $[\alpha]^{24}_D$ +42° (*c* 0.84, MeOH)) in 71% yield. Treatment of **11** with di-*tert*-butyl dicarbonate ($(Boc)_2O$) in the presence of 4-(dimethylamino)pyridine (DMAP) in acetonitrile afforded the *N*-Boc lactam **12**, which was easily ring opened by brief treatment with lithium hydroxide in aqueous THF to give the key Boc amino acid **13**.

Coupling of **13** with **2** was performed by use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[14] in the presence of triethylamine in DMF to produce the amide **14**, containing the full carbon skeleton of **1**, in 70% yield. Transformation of the nitrile function of **14** to a carboxyl group was achieved by use of the intramolecular Pinner reaction as follows. Treatment of **14** with 5% hydrogen chloride-MeOH in the presence of trimethyl orthoformate under strictly anhydrous conditions generated the imino lactone hydrochloride **15**, which was directly subjected to hydrolysis of the imino function with water. Selective ring opening[5] of the five-membered lactone function with 0.1 N NaOH at pH 9 was followed by neutralization to pH 6.5 with 0.1 N HCl.[3a,c] After purification on ion-exchange resin (Amberlite XAD-2), AI-77-B (**1**) was obtained in 76% yield from **14**. The synthetic sample ($[\alpha]^{22}_D$ −72.2° (*c* 0.07, MeOH)) was identical with the natural one ($[\alpha]^{22}_D$ −78.2° (*c* 0.08, MeOH) in every respect (TLC, NMR, FAB-MS).

Acknowledgment. This work was supported in part by the Ministry of Education, Science and Culture, Japan (a Grant-in-Aid, No. 62570948), the Japan Foundation for Optically Active Compounds, and the Terumo Life Science Foundation. We are grateful to Dr. Y. Shimojima of Asahi Chemical Industry for a generous gift of natural AI-77-B.

Supplementary Material Available: Spectra of **1**, **2**, **5a**, **5b**, and **7-14** (22 pages). Ordering information is given on any current masthead page.

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(9) In this reaction, replacement of the *N*-Boc group with benzylsulfonyl proceeded with complete diastereoselectivity. After removal of the MOM function with hydrogen chloride in methanol, the benzylsulfonyl derivative of **6** with the desired stereochemistry was obtained in 70% yield. However, deprotection of the *N*-benzylsulfonyl group was unsuccessful under various conditions.
(10) Alternative stereoselective construction of another hydroxy amino acid moiety has been achieved; see ref 1.
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Total Synthesis of "Extended" Biliverdins: The Relation between Their Conformation and Their Spectroscopic Properties

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Received September 7, 1988

Biliverdins are open chain tetrapyrrole compounds widely distributed in nature and are either free or bound to proteins.[1] All the free biliverdins have the energetically favored helical-all-syn conformation (as in **1-3**, 5*Z*-syn, 10*Z*-syn, 15*Z*-syn; Scheme I). Their absorption spectra have a ratio $\epsilon(vis)/\epsilon(UV) = 0.25$,[2] in agreement with MO calculations[3] and similar to the UV-vis absorption ratio observed in a porphyrin spectrum. In the phycobiliproteins from algae (which are light harvesting complexes[4]) the biliverdin chromophore is held in an "extended" conformation by the protein matrix. A similar situation is present in phytochrome, a plant biliprotein which governs plant morphogenesis.[5] In all these biliproteins the $\epsilon(vis)/\epsilon(UV)$ ratio of the biliverdin chromophore spectrum is greatly enhanced (about 16-fold over the ratio found in the helical-shaped conformation) since the extended bilitriene is more similar to a polyene than to a cyclic tetrapyrrole. In solution extended forms of biliverdins could only be detected as short-lived species.[6] Helicoidal (*ZZZ*)-biliverdins could be photoisomerized to their extended *EZZ* or *EZE* conformers,[7] but the latter reconverted back to their helical forms. Free biliverdins are in stable extended conformations only in the neopterobilins,[8] a group of butterfly pigments where an intramolecular addition of vinyl side chains to the pyrrole nitrogens provide rigid structures. The synthesis of a biliverdin held in the extended form by a covalent bound stilbenoparacyclophane was recently described.[9]

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