ORGANIC LETTERS

2001
Vol. 3, No. 17
2677−2680

Stereoselective Synthesis of Pseudopeptide Microbial Agent AI-77-B

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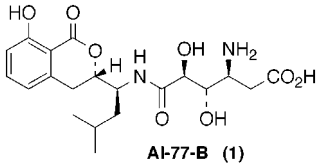
Received June 8, 2001

ABSTRACT



AI-77-B (1)

An efficient and highly stereoselective synthesis of the gastroprotective natural product AI-77-B is described. The stereocenters of the hydroxy amino acid moiety were generated by an ester-derived titanium-enolate-mediated *syn*-aldol reaction, a Curtius rearrangement, and application of Dondoni's aldehyde homologation. Condensation with the dihydroisocoumarin fragment and subsequent deprotecting transformations furnished optically active AI-77-B.

AI-77-B (**1**), a novel pseudopeptide, was isolated from the culture broth of *Bacillus pumilus* AI-77 in 1982.[1] This strongly fluorescent pseudopeptide is composed of a 3,4-dihydroisocoumarin linked to a dihydroxy-β-amino acid side chain. Its structure and absolute configuration were established by Shimojima and co-workers through spectral studies and X-ray crystallographic analysis.[2] AI-77-B represents an important drug class since it exhibits potent antiulcerogenic activity toward stress ulcers without anticholinergic, antihistaminergic, or central suppressive side effects.[2] While AI-77-B has shown very important gastroprotective properties, its therapeutic potential is limited because of poor oral absorption properties. As a result, synthetic studies and further structural modification of AI-77-B have become the subject of enormous interest. Some structure−activity studies resulted in new orally active prodrugs derived from AI-77-B, which are novel in their combined antiinflammatory and antiulcer activities.[3,4]

A number of total syntheses of AI-77-B and synthetic approaches to either the dihydroisocoumarin or the hydroxyamino acid moiety have now been reported.[5,6] We recently reported a stereoselective route to the dihydroisocoumarin fragment by a regiospecific Diels−Alder reaction of 1-methoxy-1,3-cyclohexadiene and an alkynic ester derivative which was prepared stereoselectively from *N*-Boc-L-leucinal.[7] The dihydroxyamino acid moiety has now been synthesized using an ester-derived titanium-enolate-mediated *syn*-aldol reaction, a Curtius rearrangement, and Dondoni's

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10.1021/ol0101279 CCC: $20.00
Published on Web 08/03/2001

aldehyde homologation as the key steps. Herein, we report a convergent and highly stereocontrolled total synthesis of AI-77-B in which four of the five stereogenic centers have been set by asymmetric synthesis.

Our synthetic plan for AI-77-B (**1**) is outlined in Figure 1. Retrosynthetically, assembly of AI-77-B can be carried

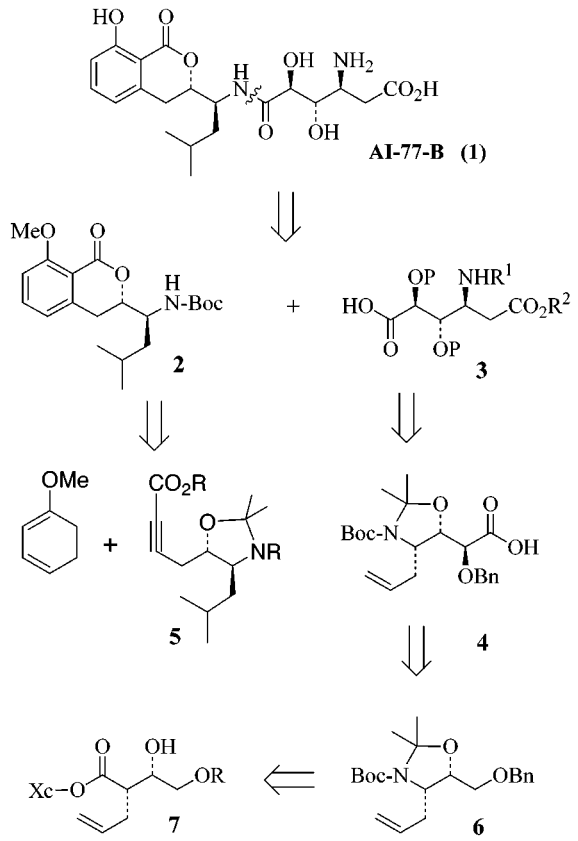
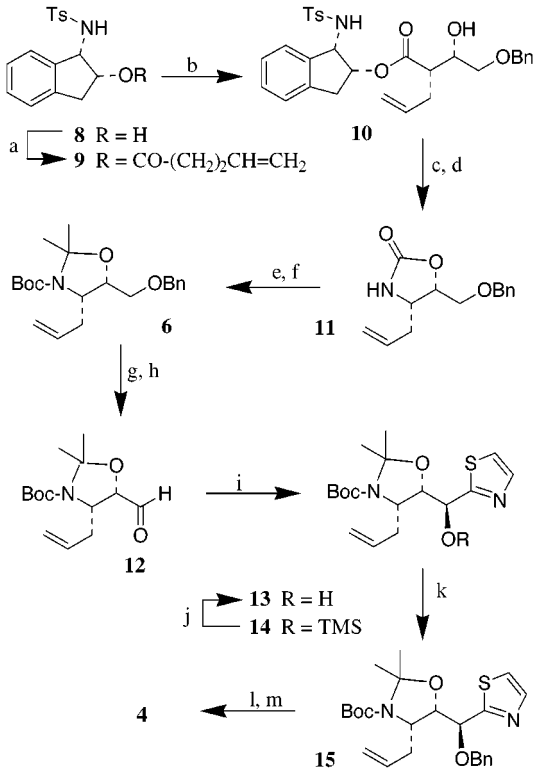


Figure 1.

out by coupling of dihydroisocoumarin fragment **2** and dihydroxyamino acid **3**. The synthesis of β-amino acid **3** could be generated from isopropylidene derivative **4** by oxidative cleavage of the terminal olefin. The α-hydroxy acid of **4** would be elaborated via stereoselective addition to the corresponding aldehyde derived from **6**. Protected amino alcohol **6** would be obtained from the corresponding β-hydroxy acid of **7** by a Curtius rearrangement. The stereocenters of **7** can be set by an asymmetric *syn*-selective aldol reaction. An optically active synthesis of the dihydroisocoumarin segment (**2**) has already been achieved using a Diels−Alder reaction of 1-methoxy-1,3-cyclohexadiene and acetylenic ester derivative **5**.[7]

As shown in Scheme 1, we planned to utilize an ester-derived titanium-enolate-mediated *syn*-aldol reaction with benzyloxyacetaldehyde to install both stereocenters of aldolate **7**.[8] Accordingly, acylation of (−)-(1*S*,2*R*)-1-(*N*-tosylamino)-2-indanol **8** with 4-pentenoic acid was carried out with DCC and DMAP to furnish ester **9** in nearly quantitative yield.[8c] Exposure of **9** to $TiCl_4$ and *N*,*N*-diisopropylethylamine in CH_2Cl_2 at 23 °C generated the corresponding titanium-enolate. Reaction of the resulting enolate with benzyloxyacetaldehyde at −78 °C furnished *syn*-aldolate **10** as a single diastereomer in 97% yield after silica gel chromatography. Ester hydrolysis with lithium hydroxide in the presence of hydrogen peroxide in a mixture of THF and water (3:1) gave the corresponding β-hydroxy acid. Chiral auxiliary **8** was recovered without loss of optical purity (92% recovery). Conversion of the β-hydroxy acid to oxazolidinone **11** was then accomplished by a Curtius rearrangement.[9] The acid was reacted with diphenylphosphoryl azide and triethylamine in CH_2Cl_2, and the resulting mixture was heated at

Scheme 1[a]



[a] (a) 4-Pentenoic acid, DCC, DMAP, CH_2Cl_2, 23 °C (99%); (b) $TiCl_4$, $^iPrNEt_2$, 0−23 °C, 1 h, then $BnOCH_2CHO$, −78 °C, 20 min (97%); (c) LiOH, H_2O_2, THF−H_2O (3:1), 23 °C 12 h (96%); (d) DPPA, NEt_3, CH_2Cl_2, reflux, 12 h (92%); (e) Boc_2O, NEt_3, DMAP, THF, 23 °C, 2 h, then aqueous NaOH−EtOH (1:1) (96%); (f) DMP, TsOH, CH_2Cl_2, 23 °C, 6 h (92%); (g) Li/NH_3, THF, −33 °C, 5 min (95%); (h) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, − 78° to 0 °C (95%); (i) 2-TST, CH_2Cl_2, 23 °C, 6 h (85%); (j) $^nBu4N^+F^-$, THF, 23 °C, 20 min; (k) NaH, BnBr, $^nBu_4N^+I^-$, THF, 12 h (95%); (l) MeOTf, 4 Å MS, MeCN, 23 °C, 30 min, $NaBH_4$, MeOH, 0 °C, 30 min, then CuO, $CuCl_2{\cdot}H_2O$, MeCN−H_2O (10:1), 23 °C, 10 min (82%); (m) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methyl-2-butene, ^{t}BuOH−H_2O (5:1) (98%).

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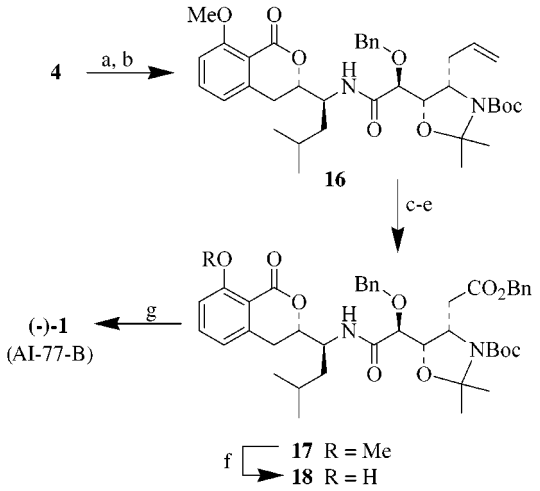
reflux for 12 h to afford oxazolidinone derivative **11** in 92% yield as a single isomer by ^{1}H and ^{13}C NMR analysis.[10] Treatment of **11** with Boc_2O and triethylamine in the presence of a catalytic amount of DMAP in THF at 23 °C for 2 h and subsequent hydrolysis of the *N*-Boc-oxazolidinone derivative with sodium hydroxide in a mixture of EtOH and water (1:1) provided the *N*-Boc-protected amino alcohol in 96% yield. Protection of the amino alcohol as *N*,*O*-isopropylidene using 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH in CH_2Cl_2 at 23 °C afforded acetonide **6** in 92% yield. Reductive cleavage of the benzyl ether was achieved by exposure of **6** to lithium in liquid ammonia at −33 °C for 5 min. The resulting alcohol was then oxidized to aldehyde **12** under Swern conditions. Stereoselective homologation of **12** was carried out by a procedure developed by Dondoni and co-workers.[11] Treatment of **12** with 2-(trimethylsilyl)thiazole in CH_2Cl_2 at 23 °C for 6 h yielded a 1:1 mixture of alcohol **13** and TMS derivative **14**. Exposure of the reaction mixture to nBu$_4$N$^+$F$^-$ for 20 min afforded **13** in 85% yield as a single diastereomer by ^{1}H and ^{13}C NMR analysis.

Our synthesis now required the conversion of the thiazole moiety into an aldehyde followed by oxidation of the aldehyde to acid **4**. Thus, benzylation of alcohol **13** with sodium hydride and benzyl bromide in the presence of tetrabutylammonium iodide yielded benzyl ether **15** in 95% yield. Transformation of the thiazole into an aldehyde was carried out in a one-pot, three-step sequence developed by Dondoni.[11] Hence, α-benzyloxythiazole **15** was first *N*-methylated by treatment with methyl trifluoromethanesulfonate in the presence of molecular sieves in acetonitrile for 30 min at 23 °C. Subsequent reduction of the thiazolinium C═N bond with sodium borohydride in MeOH at 0 °C for 30 min followed by removal of the thiazolidine by use of copper(II) oxide and copper(II) chloride in a mixture of acetonitrile and water (10:1) furnished the α-benzyloxyaldehyde in an overall yield of 82%. The more commonly used mercury(II) chloride converted the thiazolidine to α-benzyloxyaldehyde in only modest yields (25−35%). Oxidation of the aldehyde with sodium chlorite in a mixture of *tert*-butyl alcohol and water (5:1) and in the presence of 2-methyl-2-butene afforded acid **4** in 98% yield.

With the readily available isocoumarin fragment **2** and acid **4**, we then set out to couple these fragments as shown in Scheme 2. Since the free amine of isocoumarin **2** is known to form the corresponding lactam upon standing, we elected to carry out the coupling immediately after removal of the *N*-Boc group.[2a] Thus, Boc-derivative **2** was treated with neat trifluoroacetic acid at 0 °C for 30 min, the mixture was concentrated to dryness, and the resulting amine salt was reacted with acid **4** in the presence of EDCI and DMAP in CH_2Cl_2 at 23 °C for 12 h. The coupling reaction proceeded nicely under this protocol, and amide derivative **16** was

Scheme 2[a]



[a] (a) **2**, CF_3CO_2H, CH_2Cl_2, 0 °C, 30 min; (b) **4**, EDCI, DMAP, CH_2Cl_2, 23 °C, 12 h (72%); (c) O_3, CH_2Cl_2, −78 to 23 °C; (d) $NaClO_2$, 2-methyl-2-butene, $NaH_2PO_4 \cdot H_2O$, ^{t}BuOH−H_2O (5:1); (e) Cs_2CO_3, MeOH−H_2O (5:1), 30 min, BnBr, DMF, 0 °C, 6 h (87%); (f) MgI_2, THF, reflux, 5 min (93%); (g) H_2, 10% Pd/C, Dowex 50-X8, THF−MeOH (1:1), 23 °C, 12 h (75%).

obtained in 72% yield. Ozonolysis of the terminal alkene at −78 °C furnished the corresponding aldehyde. Exposure of the resulting aldehyde to sodium chlorite in a mixture of *tert*-butyl alcohol and water (5:1) in the presence of 2-methyl-2-butene furnished the corresponding acid. Reaction of this acid with cesium carbonate and benzyl bromide afforded benzyl ester **17** in 87% yield in a three-step sequence from **16**. The benzyl ester protection was necessary to allow clean *O*-demethylation in a subsequent step. Treatment of **17** with magnesium iodide in THF followed by heating of the resulting mixture at reflux furnished smooth *O*-demethylation, and phenol derivative **18** was isolated in 93% yield.[5c,12] In contrast, attempted demethylation in the presence of unprotected acid resulted in substantially lower yields (15−25%).

To complete the synthesis, we now needed to remove the remaining protecting groups. Our initial attempts at sequential removal of the remaining protecting groups proved to be more difficult than we had expected. After much effort, we optimized conditions to effect deprotection of all three protecting groups conveniently in a one-pot procedure. Exposure of **18** in a mixture of THF and MeOH (1:1) to Pd/C and Dowex 50-X8 resin at 23 °C under a hyrogen atmosphere resulted in clean removal of the isopropylidene, *tert*-butoxycarbonyl, and benzyl groups. This procedure rendered optically active AI-77-B in 75% yield ($[\alpha]^{23}_D$ = −75.2 (*c* 0.11, MeOH); lit.[5g,h] $[\alpha]^{22}_D$ = −78.2 (*c* 0.08, MeOH); mp 134−135 °C; lit.[2a] mp 139.5 °C). Spectral data for synthetic (−)-**1** are in full accordance with the reported data for authentic samples.[2a,5b,c]

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In summary, a stereocontrolled synthesis of the gastroprotective substance AI-77-B has been accomplished. Four of the five stereogenic centers of (−)-**1** were set by asymmetric syntheses. The synthesis utilized an ester- derived stereoselective aldol reaction, a regioselective Diels−Alder reaction, and Dondini homologation as the key steps. The present synthesis will provide convenient access to structural analogues of AI-77B.

Acknowledgment. Financial support by the National Institutes of Health is gratefully acknowledged.

Supporting Information Available: Spectral data (^{1}H NMR and ^{13}C NMR) for compounds **1**, **2**, **4**, **6**, **9**−**13**, and **15**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0101279