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Stereoselective Synthesis of Dihydroisocoumarin Moiety of Microbial Agent AI-77-B: a Diels-Alder Based Strategy

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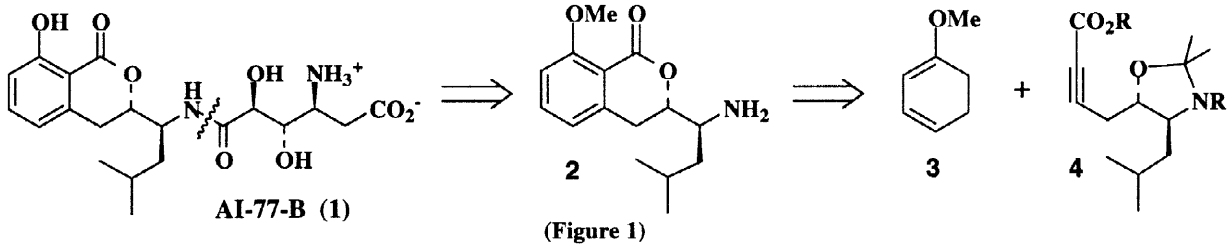
Abstract: The dihydroisocoumarin fragment of the gastroprotective natural product AI-77-B has been synthesized in optically active form by using a regiospecific Diels-Alder reaction of 1-methoxy-1,3-cyclohexadiene and an acetylenic ester derivative, prepared stereoselectively from leucinal.

The 3,4-dihydroisocoumarins are important structural features for many biologically active natural products.[1] A member of this class is AI-77-B, which contains a dihydroisocoumarin linked to a hydroxylated amino acid side chain. This pseudopeptide was isolated from the culture broth of *Bacillus pumillus* AI-77 in 1982.[2] The structure and absolute configuration of AI-77-B were established by Shimojima and co-workers through spectral studies and X-ray crystallographic analysis.[2] AI-77-B represents a unique drug class since it has shown potent antiulcerogenic activity towards stress ulcers without any anticholinergic, antihistaminergic or central suppressive effects.[3] In view of its significance as a gastroprotective agent, synthetic studies and further structural modification of AI-77-B has become the subject of immense interest over the years. Already, a number of total syntheses as well as several partial syntheses of AI-77-B have been reported.[4, 5] Thus far, the major strategy for the construction of the dihydroisocoumarin segment has been the addition of anions derived from ortho-toluyl ester or oxazoline to protected leucinal. This approach generally results in a mixture of epimers at the C-3 position.[4] Herein, we report a stereoselective route to the dihydroisocoumarin segment of AI-77-B by a regiospecific Diels-Alder reaction of 1-methoxy-1,3-cyclohexadiene and substituted acetylenic ester derivative as a dienophile. Both the natural C-3(*S*)-configuration and its epimer have been generated diastereoselectively by allyl-metal or propargyl-metal addition to leucinal.[6, 7]



AI-77-B (1) 2 3 4

(Figure 1)

As depicted in Figure 1, we planned to construct the dihydroisocoumarin skeleton by a Diels-Alder reaction as the key step. Thermal Diels-Alder reactions of 1-methoxy-1,3-cyclohexadiene and

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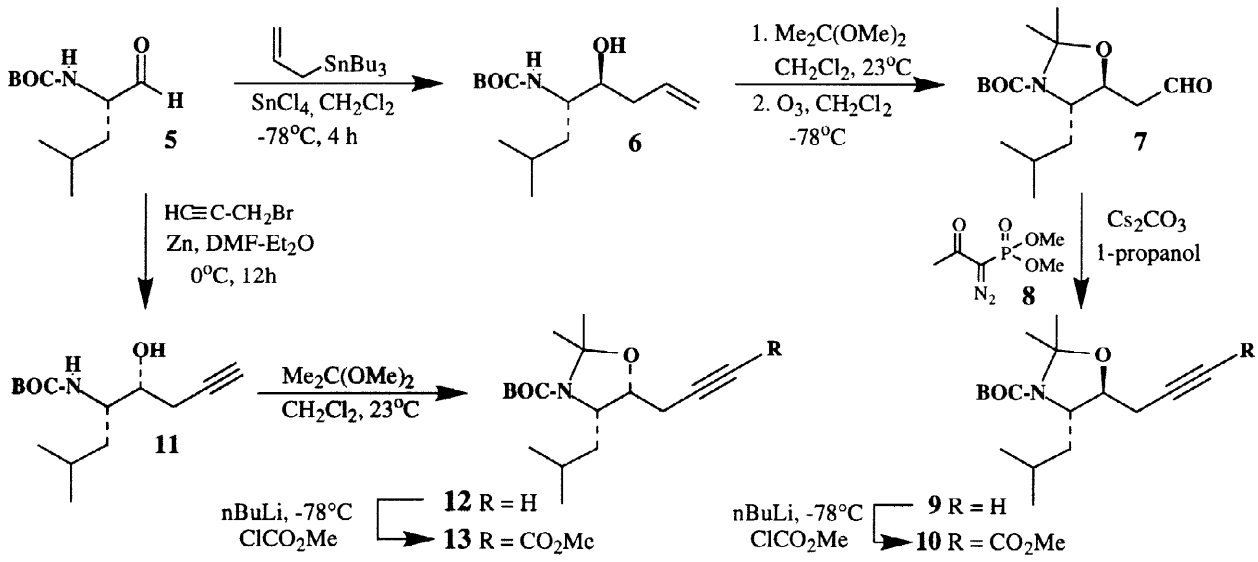
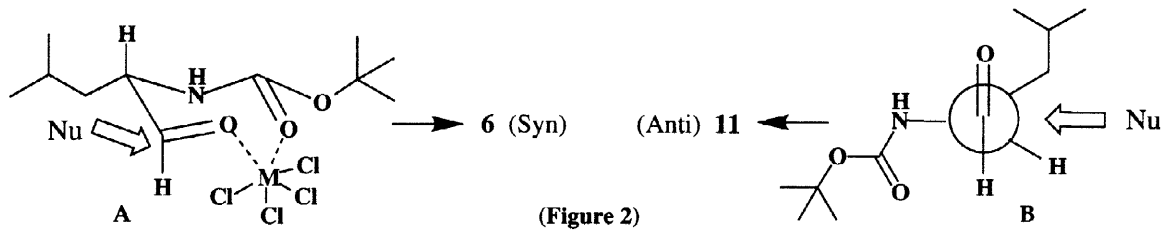
acetylenes have been shown to proceed with extrusion of ethylene providing aromatic compounds conveniently. This strategy has been utilized for the syntheses of mellein, phthalates and phenols.[8] For the synthesis of dihydroisocoumarin fragment **2**, we first synthesized the acetylenic substrate stereoselectively. As shown in Scheme 1, the known *N*-BOC-leucinal **5** was prepared in multigram scale by LAH reduction of the corresponding Weinreb amide.[9] Treatment of **5** with 2 equiv of $SnCl_4$ at -78°C followed by dropwise addition of allyltributyltin in CH_2Cl_2 provided the homoallylic alcohol

Scheme 1



6 in 60% yield as a 14:1 mixture of diastereomers by ^{13}C-NMR analysis. The reaction of **5** with allyltrimethylsilane in the presence of $SnCl_4$ at -78°C has also resulted in **6** with comparable diastereoselectivities.[6b] The stereochemical assignment of alcohol **6** was based upon a chelated transition state model **A** shown in Figure 2. Such allyl metal addition to α-aminoaldehydes has been previously studied by Kiyooka *et al* and Rich *et al.*[6] Homoallylic alcohol **6** was converted to protected aldehyde **7** by treatment with dimethoxypropane in the presence of a catalytic amount of *p*-TsOH at 23°C for 12 h followed by ozonolytic cleavage of the resulting olefin at -78°C



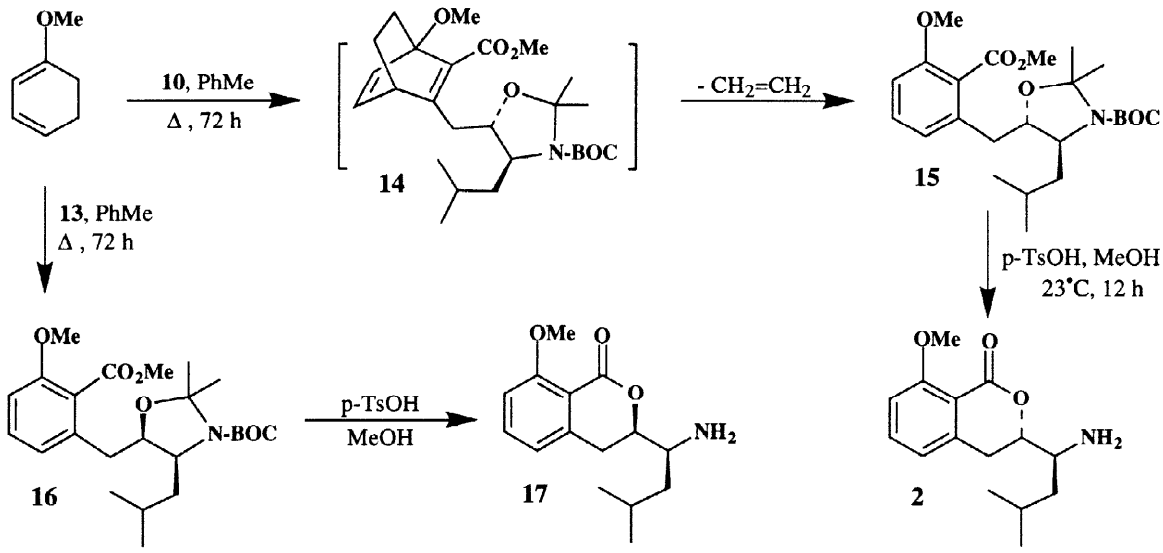
(Figure 2)

(76% from **6**). The ^{13}C-NMR analysis revealed the presence of a single diastereomer at this point. Installation of the acetylenic functionality was accomplished by exposure of the aldehyde **7** to 1.5 equiv of 1-diazo-2-oxopropyl phosphonate **8**[10] in propanol followed by addition of 2 equiv of Cs_2CO_3

at 0° - 23°C for 12 h. The reaction proceeded smoothly providing the acetylene derivative **9** in 82% yield after silica gel chromatography. Acetylene **9** was then deprotonated with 1.5 equiv of n-BuLi in THF at -78°C for 1 h and the resulting lithium acetylide was treated with methyl chloroformate at -78°C to furnish the acetylenic ester **10** in 86% yield. The corresponding C-3 epimer **13** was synthesized stereoselectively by an alternative route. Thus, *N*-BOC-Leucinal **5** in a mixture (1:1) of DMF and Et_2O at 0°C, was treated with 4 equiv of propargyl bromide followed by slow addition of zinc dust at 0°C.[7] The resulting mixture was allowed to stir at 0° to 23°C for 12 h to provide the homopropargylic alcohol **11** in 62% yield after silica gel chromatography. The ^{1}H-NMR and ^{13}C-NMR analysis revealed the presence of a single diastereomer. The stereochemical course of such reaction can be explained by a Felkin-type transition-state model **B** in which addition takes place anti to the polar C-N bond as depicted in Figure 2.[11] The BOC-aminoalcohol **11** was protected as the isopropylidene derivative by treatment with dimethoxypropane in the presence of a catalytic amount of *p*-TsOH at 23°C to furnish **12** in 95% yield. Acetylene **12** was converted to acetylenic ester **13** as a single diastereomer in 85% yield as described above.

The Diels-Alder reaction of acetylenic ester **10** with excess of 1-methoxy-1,3- cyclohexadiene **3** (10 equiv) was carried out in toluene in a sealed tube at 175°C bath temperature for 72 h (Scheme 2). The cycloaddition proceeded with the extrusion of ethylene to provide the benzoate derivative **15** in 73% yield after silica gel chromatography. Exposure of benzoate derivative **15** to a catalytic

Scheme 2



amount of *p*-TsOH in MeOH at 23°C for 12 h resulted in the 3,4-dihydroisocoumarin derivative **2** (α_D^{23} = -45.33; c, 0.8, CH_3OH) of AI-77-B. The spectral properties of **2** are in full agreement with the reported data.[5c] For the synthesis of the C-3 epimer, cycloaddition of **3** with dienophile **13** was carried out under similar conditions to furnish the cycloadduct **16** in 84% yield. Treatment of **16** with *p*-TsOH in MeOH afforded the epimeric dihydroisocoumarin derivative **17** (α_D^{23} = +81.5; c, 2.92, CH_3OH) in quantitative yield.[12]

In summary, the 'western' fragment of the antiulcer agent AI-77-B has been synthesized using a regiospecific Diels-Alder reaction as the key step. The route allows the diastereoselective synthesis of 3,4-dihydroisocoumarin derivative **2** or its C-3 epimer **17** from *N*-BOC-leucinal. Further synthetic studies of AI-77-B are currently under investigation.

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12. All new compounds gave satisfactory spectroscopic and analytical results. **Product 2:** ^{1}H NMR (400 MHz): δ, 7.43 (t, 1H, J=7.9 Hz), 6.89 (d, 1H, J=8.5 Hz), 6.80 (d, 1H, J=7.48 Hz), 4.19-4.14 (m, 1H), 3.93 (s, 3H), 3.11 (dd, 1H, J=12.7, 15.7 Hz), 2.99-2.94 (m, 1H), 2.78 (dd, 1H, J=2.5, 16.0 Hz), 1.79-1.75 (m, 1H), 1.41-1.37 (m, 2H), 0.933 (d, 3H, J=6.5 Hz), 0.897 (d, 3H, J=6.5 Hz); ^{13}C NMR (100 MHz): δ, 162.48, 161.02, 142.03, 134.42, 119.28, 113.63, 110.69, 81.65, 56.08, 51.81, 42.53, 31.44, 24.32, 23.54, 21.41. MS, mass (CI) m/z 264 (M^{+}+ H); **Product 17:** ^{1}H NMR (400 MHz): δ, 7.42 (t, 1H, J= 7.9 Hz), 6.88 (d, 1H, J=8.4 Hz), 6.81 (d, 1H, 7.5 Hz), 4.26-4.21 (m, 1H), 3.91 (s, 3H), 3.25-3.21 (m, 1H), 3.12 (dd, 1H, J=12.6, 15.9 Hz), 2.72 (dd, 1H, 2.4, 16.1 Hz), 1.76-1.69 (m, 1H), 1.31-1.27 (m, 2H), 0.934 (d, 3H, J=6.5 Hz), 0.891 (d, 3H, 6.5 Hz); ^{13}C NMR (50 MHZ): δ, 162.45, 161.08, 142.15, 134.36, 119.45, 113.65, 110.67, 81.57, 56.04, 50.77, 41.59, 28.44, 24.57, 23.44, 21.52. MS, mass (CI) m/z 264 (M^{+}+ H).