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A New Enantioselective Synthesis of the Aminodihydroisocoumarin Moiety of AI-77-B

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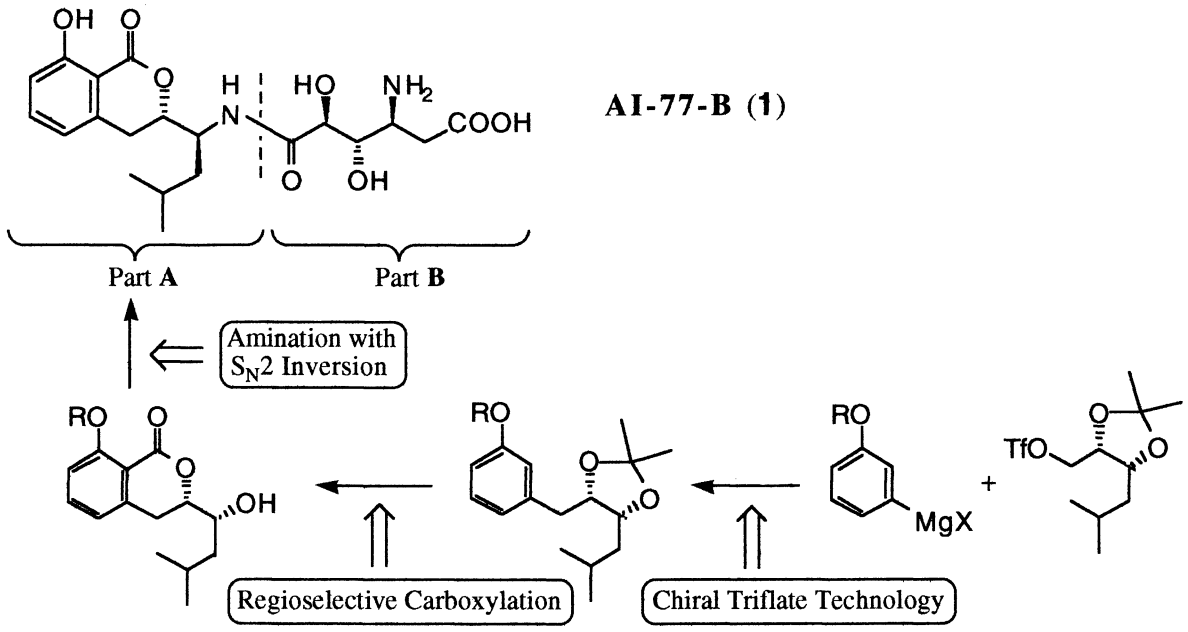
The aminodihydroisocoumarin moiety of AI-77-B, a gastroprotective substance isolated from *Bacillus pumilus* AI-77, has been prepared from a convenient chiral synthon of L-erythrose by combination of chiral triflate technology and regioselective aromatic carboxylation.

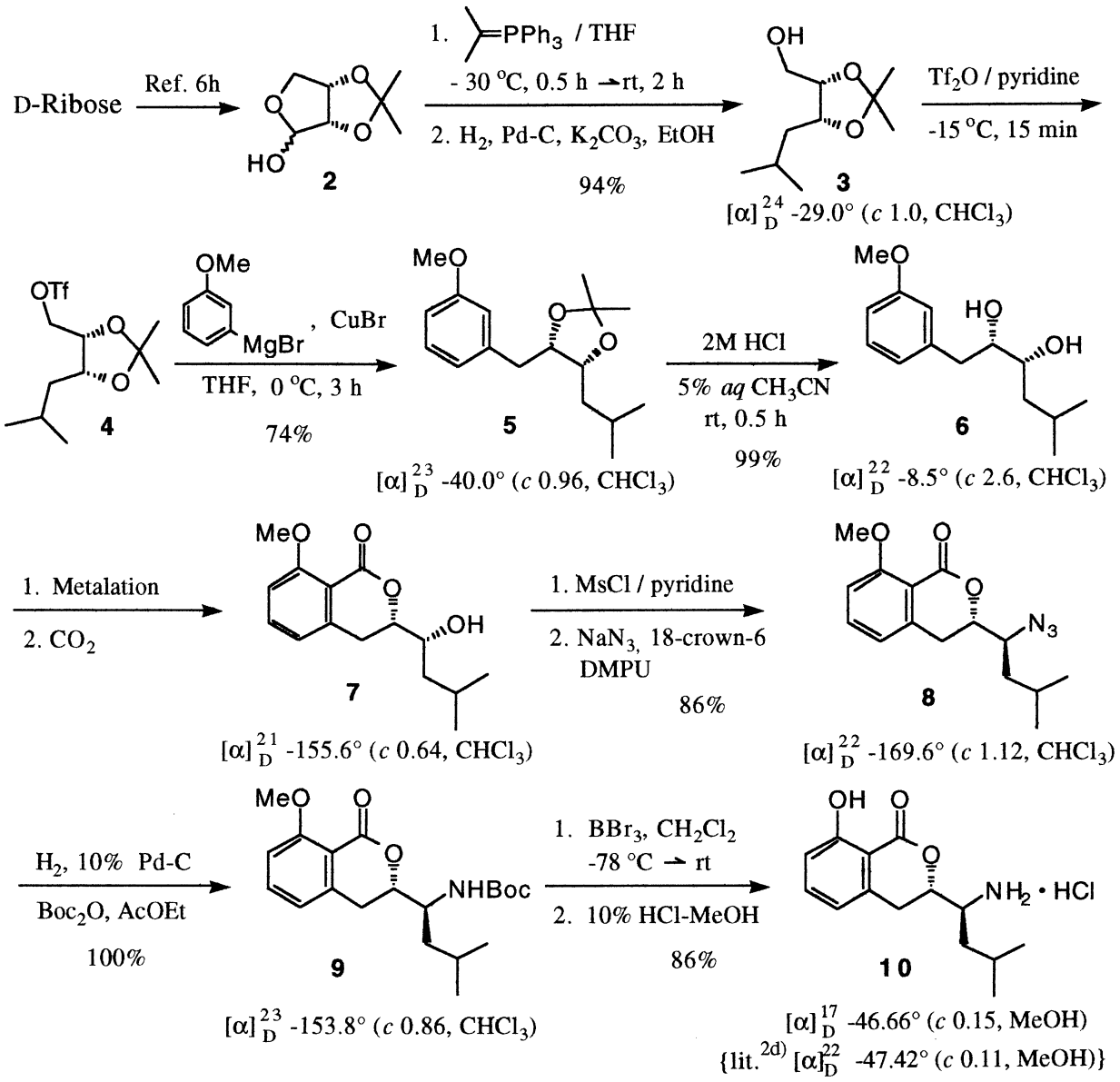
AI-77-B (**1**) is a unique dipeptide isolated from a culture broth of *Bacillus pumilus* AI-77 as a gastroprotective substance.[1] Recently, the total synthesis of this compound has been disclosed by Shioiri's[2] and Thomas'[3] groups.[4] Synthetically, AI-77-B (**1**) can be divided into two segments, *i.e.*, the aminodihydroisocoumarin part **A** and the hydroxyamino acid part **B** and these compounds containing amino acid functionalities are usually elaborated from naturally occurring amino acids as chiral sources.[5] In our continuing interest to explore the synthetic utility of chiral triflate technology,[6] herein we wish to describe a conceptually different approach to the aminodihydroisocoumarin moiety **A**[7] by taking advantage of carbohydrate-derived chiral synthons.[8] Thus, our retrosynthetic strategy is based on a successful combination of chiral triflate technology, regioselective aromatic carboxylation, and amination with S_N2 inversion (Scheme 1).



Scheme 1.

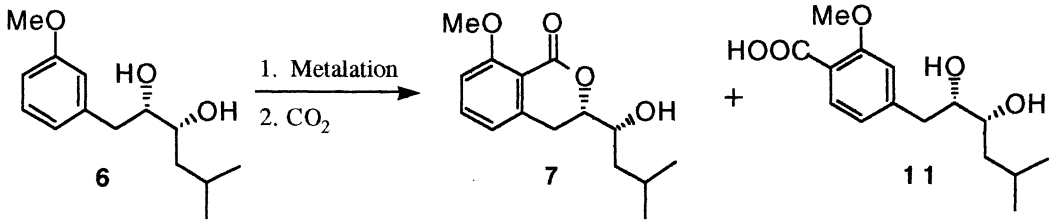
The synthesis starting from 2,3-*O*-isopropylidene-L-erythrose (**2**), which is readily accessible from D-ribose,[6h] is illustrated in Scheme 2.[9] The isopropyl unit in **3** was incorporated by the Wittig reaction with isopropylidene triphenylphosphorane followed by catalytic hydrogenation in 94% yield. Triflation followed by coupling reaction with 3-methoxyphenylmagnesium bromide in the presence of cuprous bromide gave **5** in 74% yield. After deprotection of an acetonide group under carefully controlled conditions,[10] the resultant diol **6**, mp 93.5-94.0 °C, was further subjected to the regioselective carboxylation.

Since the regioselective ortho metalation/carboxylation of aromatic ethers has been accepted as a general means in aromatic chemistry,[11] we expected that the application of this technique to **6** should enable us to obtain the desired dihydroisocoumarin **7** with relative ease.[12] Unexpectedly, however, we found that a crucial step for this carboxylation was rather difficult and the reaction course was highly depend on the metalation conditions. Some representative results are compiled in Table 1.



Scheme 2.

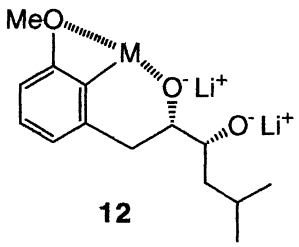
Table 1. Regioselective Aromatic Carboxylation of Diol **6**



Metalation conditions	Product yields / %
n-BuLi (6.6 equiv.) / TMEDA (6.0 equiv.), THF, -78 °C, 1 h	no products, recovery(38)[a]
n-BuLi (3.2 equiv.) / *t*-BuOK (2.0 equiv.), THF-hexane, -78 °C, 1 h	**7**(14), **11**(45), recovery(40)
n-BuLi (6.5 equiv.) / TMEDA (6.0 equiv.), hexane, reflux, 6 h	**7**(32), **11**(35), recovery(10)

a) A considerable amount of unidentified products was obtained.

While the usual procedure employing *n*-BuLi/*N,N,N',N'*-tetramethylethylenediamine (TMEDA) at -78 °C was unsuccessful, the use of Schlosser's super base (*n*-BuLi/*t*-BuOK)[13] provided the desired product **7** along with its regioisomer **11**, albeit in low regioselectivity. Furthermore, we found that the lithiation with *n*-BuLi/TMEDA in refluxing hexane for 6 h followed by exposure to Dry-Ice yielded a mixture of **7** and **11** in 32 and 35% yield, respectively. Each regioisomer was readily separable by column chromatography and determined individually by IR and NMR measurements.[9]



12

M = Li or K

The observed results demonstrate clear evidence for the competitiveness of lithiation processes at both ortho sides of the OMe group. Initially, we thought that the formation of **7** should be favorable rather than the formation of **11**, since the intermediary formed metalated species such as **12** might be stabilized through double coordination with OMe and the proximate O^-Li^+ in analogy to the related systems.[11] However, from the fact that was observed with **6** it can be understood considering that the steric compression caused by the side chain inhibits significantly the lithiation pathway at the desired position.

In any event, with the required amount of **7** in our hand, we then proceeded with the synthesis of the target molecule. Thus, mesylation followed by treatment with sodium azide in 2,6-dimethylpropyleneurea (DMPU) gave azide **8** in 86% yield, resulting in a complete S_N2 inversion at the stereocenter bearing an azide group. Finally, **8** was transformed into the *N-tert*-butoxycarbonyl(*N*-Boc)-protected amine **9**, mp 143.5-144.5 °C, by treatment with Boc_2O under catalytic hydrogenation conditions. The absolute configuration of **9** was unambiguously confirmed by conversion into the hydrochloride salt **10**, mp 206-207 °C (lit.[2d] mp 206-207 °C) by deprotection with boron tribromide. The physical and spectral data of **10** were in good agreement with the literature data.[2d]

The synthesis of **9** as described above is expeditious and highly enantioselective and represents a considerable synthetic value of chiral triflate technology, in particular, by virtue of the contribution to chiral synthon chemistry. By utilizing the key intermediates such as **8-10** further synthetic studies on AI-77-B (**1**) are now in progress.

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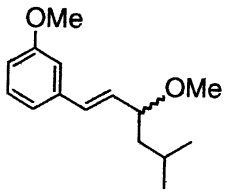
8) *Cf.* S. Hanessian, "Total Synthesis of Natural Products: The 'Chiron' Approach," Pergamon Press, Oxford (1983).

9) Satisfactory spectral and analytical data were obtained for all new compounds.

10) For example, treatment of **5** with 2 M HCl in MeOH for prolonged reaction times led only the following compound:



11) For reviews, see: H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1 (1979); V. Snieckus, *Chem. Rev.*, **90**, 879 (1990); V. Snieckus, *Pure Appl. Chem.*, **62**, 671 (1990).

12) We have also examined an alternative straightforward approach toward **7** from **4**. Full details will be reported elsewhere.

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