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APPROACHES TOWARD THE TOTAL SYNTHESES OF ASTINS A, B, AND C

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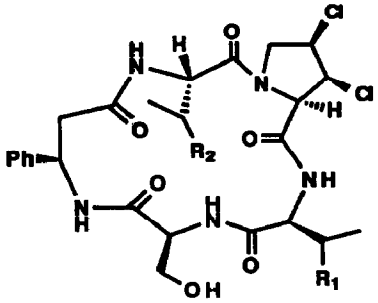
Abstract: *Two nonessential amino acids, (+)-(S)-2-aminobutanoic acid and the methyl ester of L-β-phenylalanine [(+)- (R)-3-amino-3-phenyl propanoic acid], were synthesized to provide a tripeptide which will be used in the total syntheses of astins A, B, and C.*

The isolation of three antitumor cyclic pentapeptides, astins A (**1**), B (**2**), and C (**3**),[1,2] from the medicinal plant *A. tataricus* (Compositae), known in Chinese medicine as containing several terpenoids and saponins, has prompted us to find suitable syntheses for the nonessential amino acids present in these natural products.



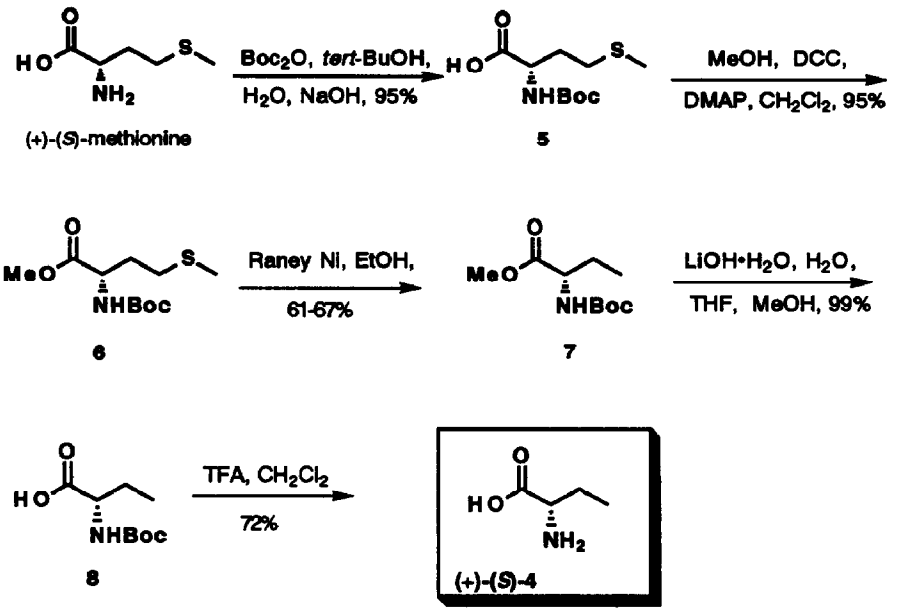
1	R_1 = H, R_2 = OH	Astin A
2	R_1 = OH, R_2 = H	Astin B
3	R_1 = H, R_2 = H	Astin C

The simplest of these nonproteinogenic amino acids is (+)-(*S*)-2-aminobutanoic acid (**4**). Although there have been other syntheses for this amino acid,[3,4-7] we believe our procedure is more convenient, high yielding and economical than previous methods. (+)-(*S*)-2-Aminobutanoic acid has been synthesized in many different ways, which include optical resolution of amino acid esters by enzymatic hydrolysis,[4,5] the oxidation of (+)-(*S*)-2-N-benzoylamino-1-butanol and (-)-(*R*)-2-N-benzoylamino-1-butanol to the corresponding acids,[3] followed by hydrolysis; the stereocontrolled addition of the cyano group to Schiff bases using a CN-modified hemin-copolymer;[6] and hydrogenation of chiral cyclic α,β-didehydroamino acid derivatives in the presence of Pd/C, followed by hydrolysis.[7]

Our approach to **4** is shown in **Scheme 1.** The amino group of (+)-(*S*)-methionine was protected as its Boc-derivative (**5**) with di-*tert*-butyl dicarbonate [$(Boc)_2O$]. The carboxylic acid group of **5** was esterified with methanol, 1,3-dicyclohexylcarbodiimide (DCC), and N,N-dimethylaminopyridine (DMAP). Freshly

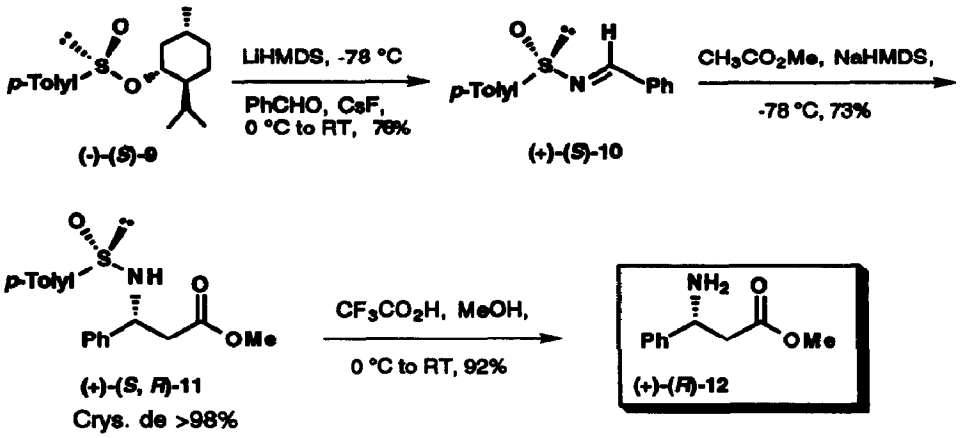
prepared Raney nickel[8] in ethanol removed the methylthio group to provide **6**. Saponification of the ester group with lithium hydroxide, followed by removal of the Boc group with trifluoroacetic acid in methylene chloride, afforded **4**. Both enantiomerically pure (+)-(*S*)-N-Boc-2-aminobutanoic acid (**8**) and (+)-(*S*)-2-aminobutanoic acid (**4**) were obtained in the present study. The optical purity of **4**, $[\alpha]_D^{20}$ =+18.6° (c=1.16, 3N HCl), was confirmed by comparison of the product's optical rotation with that of authentic sample.[9]

Scheme 1



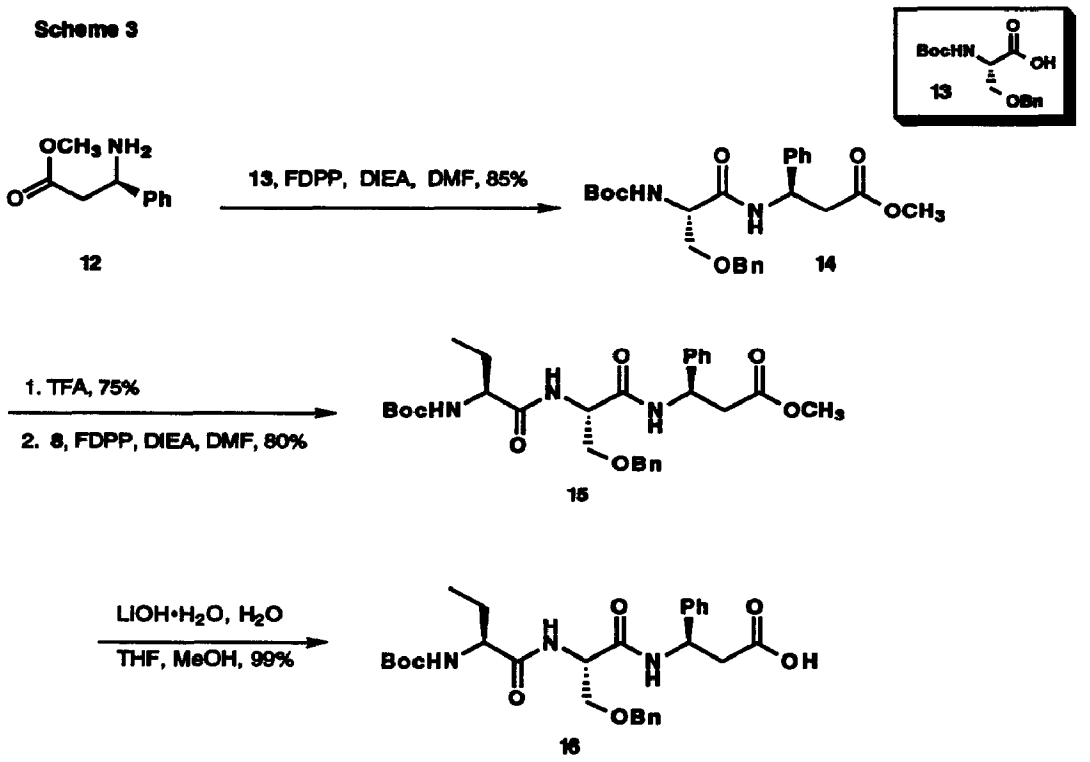
The second nonessential amino acid present in the astins is L-β-phenylalanine [(+)-(*R*)-3-amino-3-phenylpropanoic acid] (**12**), which is also found in the taxane alkaloids,[10] the alkaloid dihydroperiphylline,[11] and the peptide antibiotic andrimid.[12] The synthesis of the methyl ester of **12** is shown in **Scheme 2** and uses the chiral ammonia imine synthon (+)-(*S*)-N-(benzylidene)-*p*-toluenesulfinamide (**10**) which is prepared in 76% yield by treatment of (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (**9**) with 1.5 equivalents of lithium bis(trimethylsilyl)amide followed by reaction with 2.0 equivalents of benzaldehyde in the presence of cesium fluoride.[13] Reaction of (+)-(*S*)-**10** with 1.5 equivalents of the sodium enolate of methyl acetate (NaHMDS, methyl acetate) at -78 °C afforded (+)-(*S*,*R*)-**11** as a 96:4 diastereomeric mixture after flash chromatography. Use of the sodium enolate in place of lithium enolate, as previously reported, significantly improved the diastereoselectivity.[14,15] Enantiopure **11** (>98% de) was obtained on crystallization from *n*-hexane in 73% yield and was hydrolyzed to the methyl ester **12**, $[\alpha]_D^{20}$ =+22.3° (c=1.99, $CHCl_3$)[14] in 92% yield with 2.0 equivalents of trifluoroacetic acid in methanol.

Scheme 2



The synthesis of the tripeptide from the methyl ester of L-β-phenylalanine (**12**) is shown in Scheme 3.

Scheme 3



This amino acid ester (**12**) was coupled with N-Boc-L-Ser(OBn)OH (**13**) in 85% yield to give **14**, using

pentafluorophenyl diphenylphosphinate (FDPP)[16] and diisopropylethylamine (DIEA). Removal of the *tert*-butoxycarbonyl (Boc) group was accomplished in 75% isolated yield, using trifluoroacetic acid (TFA) in methylene chloride. The deprotected dipeptide was coupled with (+)-(*S*)-N-Boc-2-aminobutanoic acid (**8**) in 80% yield, using FDPP and DIEA. The methyl ester **15** was saponified with lithium hydroxide to provide the tripeptide **16**, $[\alpha]_D^{20}$ =+7.5 (c=1.08, $CHCl_3$), in quantitative yield. This tripeptide (**16**) and its analog with L-allo-threonine as a component will be coupled with the dipeptide of (+)-(*S*)-2-aminobutanoic acid and (3*S*,4*R*)-3,4-dichloro-L-proline to complete the total syntheses of astins A, B and C (**1**, **2** and **3**).

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8. Raney type alloy Ni-Al 50/50 powder was purchased from Alfa Products. Preparation of the aluminum-nickel catalyst : 19.5 g of sodium hydroxide was dissolved in 75 mL of water, followed by the addition of 15 g of alloy in small portions with stirring over the course of 45 min. During the addition, the temperature was kept between 75-80°C. At the end of the addition, the suspension was allowed to cooled to room temperature over the period of 75 minutes. The solids were washed until the solution was neutral and then washed with absolute ethanol three times. [Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: 1967; Vol. 1, pp 723-731.]
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