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IMPROVED SYNTHETIC ACCESS TO THE β,γ-ENOL ETHER AMINO ACIDS, L-2-AMINO-4-METHOXY-TRANS-BUT-3-ENOIC ACID AND L-2-AMINO-4-METHOXY-CIS-BUT-3-ENOIC ACID

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Summary: A synthetic route to L-2-amino-4-methoxy-trans-but-3-enoic acid, exclusive of the cis-isomer, has been developed. The key step is direct formation of a trans-enol ether derivative from the corresponding dimethylacetal, by refluxing in CCl_4, in the presence of hexamethyldisilazane and Me_3SiI. The isomeric L-cis amino acid could be accessed from this route by isomerizing the intermediate, methyl DL-2-acetamido-2-amino-4-methoxy-trans-but-3-enoate at 217° C to give a cis-trans mixture in a 1:10 ratio.

Dehydroamino acids are of particular biological interest for their properties as enzyme inhibitors,[1,2] as well as components of peptide structures.[3] The specific class of β,γ-enol ether amino acids has presented synthetic challenges arising from the need to generate an enol ether moiety in the presence of potentially reactive amino acid substituents and to deprotect the latter groups without degrading the acid sensitive enol ether substituent.

The isomeric amino acids, L-2-amino-4-methoxy-trans-but-3-enoic acid[4] (L-transAMB) and L-2-amino-4-methoxy-cis-but-3-enoic acid[2] (L-cisAMB) are representatives of this class, which also includes the naturally occurring amino acids L-2-amino-4-(2-aminomethoxy-trans-but-3-enoic acid[5] and rhizobitoxine.[6] Synthesis of this latter amino acid has relied on the use of a protected derivative of L-transAMB as a key reaction intermediate. L-transAMB was originally isolated from Pseudomonas aeruginosa.[4] Extensive biological characterization has shown it to be a potent inhibitor of ethylene biosynthesis in plants[7] and a potent inhibitor of cultured Walker 256 carcinosarcoma cells.[8] It inhibits several enzymes, including serine hydroxymethyltransferase,[9] porphobilinogen synthase,[10] δ-aminolevulinic acid synthetase,[11] δ-aminolevulinic acid dehydrase[11] and L-aspartate amino transferase.[1] It was demonstrated to be a potent irreversible k_{cat} inhibitor of the latter enzyme, suggesting that other β,γ-unsaturated amino acids might similarly inhibit related pyridoxal-linked enzymes.

L-cisAMB, originally obtained as a minor component of L-transAMB synthesis,[2,12] has also proved to be of considerable biological interest. It is a potent methionine analog inhibitor of S-adenosylmethionine (AdoMet) synthetase[2] and has been used to study the biochemical consequences of AdoMet depletion in cells.[13,14,15] Its antitumor activity has also been evaluated.[16]

The original preparation of these two isomeric amino acids utilized a synthetic route in which the key step was pyrolysis of a labile hemiacetal ester derivative 3, to give a cis-trans mixture of 4, which, after decarbethoxylation, gave 5 and 6 in a 1:3 cis-trans ratio.[2,12] Chromatographic separation, followed by enzymatic resolution, has consistently provided L-transAMB and L-cisAMB in respective overall yields of 9.5% and 1.6% in our scale-up preparations. More recently, syntheses of 5[17] and 6,[18] exclusive of each other, have been reported. Both utilize a convergent strategy to obtain the desired cis- or trans-intermediate, although in the case of 6, the key step is the isomerisation of an α,β-dehydroamino acid derivative to give the trans-isomer, stereoselectively. The new route to L-transAMB[18] provides versatility with regard to the introduction of different enol ether groups and N-protective groups, but requires at least nine synthetic steps to obtain the penultimate intermediate 6. The new route to 5 provides a means to obtain L-cisAMB without the necessity of tedious chromatographic separations of protected cis-trans intermediates, but significant improvements in the final yield of the L-amino acid were not realized because of a low yield in the key condensation step.

Novel methods to improve synthetic access to L-cisAMB and L-transAMB remain of interest from both a chemical and a biological viewpoint. In this regard, we have developed modifications of the synthesis by Keith et al.,[12] which make this original synthetic strategy more attractive for obtaining either of these isomeric amino acids: one modification provides N-Ac-DL-transAMB methyl ester 6, stereoselectively; the second modification provides access to additional quantities of N-Ac-DL-cisAMB methyl ester 5 from the pure trans-isomer, 6. As shown in the accompanying synthetic scheme, 7 could be obtained directly from the dimethyl acetal 2 (2.3 g) in 77% yield, by refluxing in CCl_4 with trimethylsilyl iodide (Me_3SiI, 1.2 equiv) and hexamethyldisilazane (HMDS, 2.5 equiv) for 4 hr, a procedure adapted from Miller and McKean's general method for facile preparation of methyl enol ethers from acetals.[19] In addition, we were able to isomerize pure 6 by heating at 217° C (for 1.5 hr under an argon atmosphere), to give a mixture of 5 and 6 in a cis-trans ratio of 1:10. Since pure 6 could be recovered (72%), significant quantities of 5 were accumulated for the final resolution step by repetitive isomerization and chromatography, albeit in a tedious manner. These two modifications provide easier access to both L-cisAMB and/or L-transAMB and as a result, enhance the versatility of the original synthetic route which can more readily accommodate the need for increased amounts of either isomeric amino acid.

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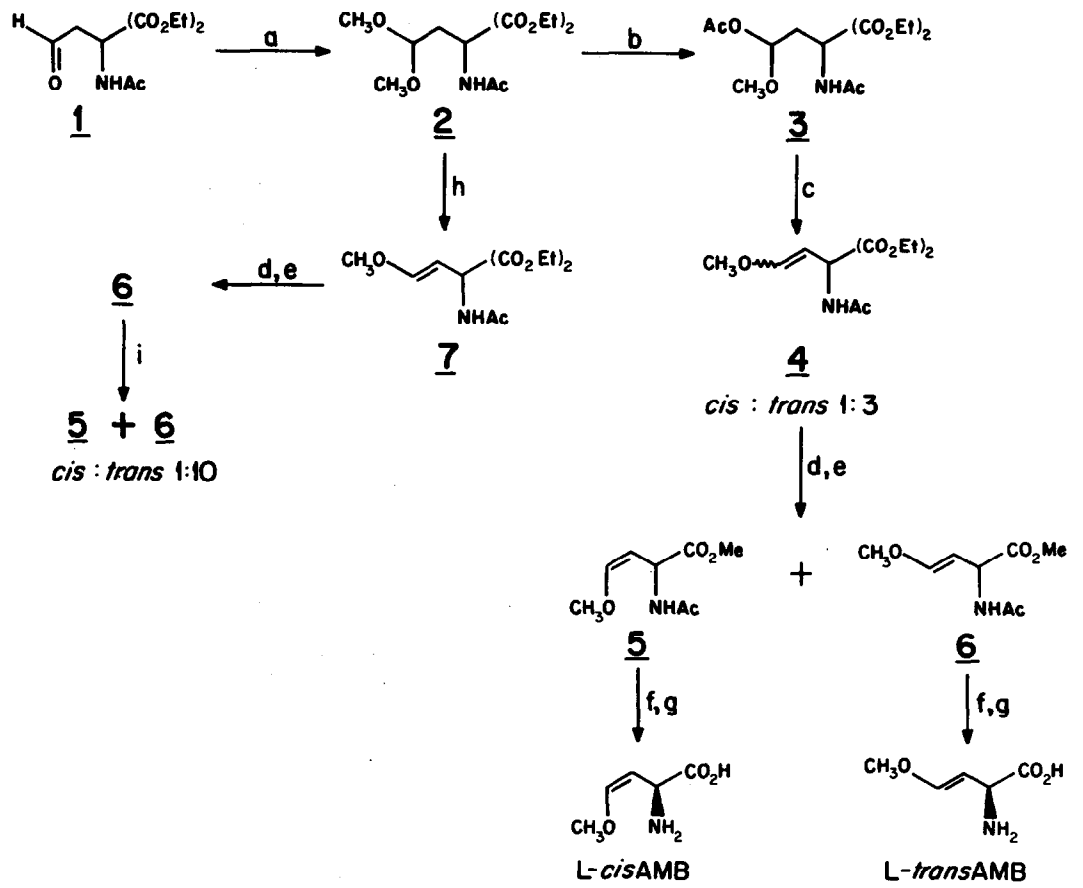
Scheme



(a) $(MeO)_3CH$, NH_4Cl, reflux (b) Ac_2O, Dowex 50-X8 (H^+), 65° C (c) 185° C, 17mm (d) NaOMe, MeOH, RT (e) chromatography (f) aq. LiOH (g) hog kidney acylase I, 40° C, pH 7.4, 16 h (h) Me_3SiI, HMDS, CCl_4, reflux, 4 h (i) 217° C, argon, 1.5 h.

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