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Enantio- and Diastereoselective Synthesis of (*R*, *R*)- β -Methoxytyrosine

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Abstract

The nonproteinogenic amino acid (2*R*,3*R*)- β -Methoxytyrosine, a constituent of several cyclic depsipeptide natural products, was synthesized in protected form (**8**) from a readily available cinnamate ester in four steps and 62% overall yield with a greater than 28:1 *er* and 19:1 *dr*. This method provides a highly efficient, enantio- and diastereoselective synthesis of an important amino acid.

The nonproteinogenic amino acid (2*R*,3*R*)- β -methoxytyrosine (**1**, Figure 1) is found in the cyclic depsipeptide natural products callipeltin A¹ (**2**), papuamides A (**3**) and B² (**4**). All of these related natural products were shown to possess potent anti-HIV activity and broad spectrum cytotoxicity.^{1,2} The interesting biological activities and complex structures of **2–4** have attracted the attention of the synthetic community, thus requiring an efficient synthesis of **1**. Because the configuration of **1** could not be determined during the initial structural studies of **2–4**, initial synthetic efforts by our group³ and others⁴ usually focused on the production of multiple isomers of β -methoxytyrosine ranging from moderate to high stereoselectivity. More recently, work done by our group³ and others^{4b,5} has conclusively proved that the configuration of β -methoxytyrosine in **2–4** is (2*R*,3*R*). In light of this information, it was our objective to develop an efficient, enantio- and diastereoselective synthesis of **1**.

Evans has previously shown that cinnamate esters undergo asymmetric aziridination using chiral bis(oxazoline)-copper complexes, which can be followed by diastereoselective ring opening to form phenylalanine derivatives.⁶ It was envisaged that this strategy could be used to synthesize **1** in highly stereocontrolled fashion.

The synthesis began (Scheme 1) by aziridination of *p*-coumarate TBS ether⁷ with Cu(OTf)₂ and (–)-2,2'-isopropylidenebis[(4*S*)-4-phenyl-2-oxazoline] as the catalyst/ligand system, PhINNs⁸ (*N*-(*p*-nitrophenylsulfonyl)iminophenylidodane) as the nitrene source, and dichloromethane as the solvent. The reaction is judged to be complete and filtered to remove the copper as soon as all of the PhINNs dissolves; allowing the reaction to run longer results in the formation of side products. The aziridine is then dissolved in methanol to form **6** in 89% yield with a greater than 19:1 *dr* and 28:1 *er*.⁹

PhINNs is used as the limiting reagent in the aziridination reaction with excess alkene present to help ensure consumption of reagent. If the alkene is used as the limiting reagent the yield decreases to 40% and greater amounts of side products form. The more commonly used PhINTs (*N*-(*p*-toluenesulfonyl)iminophenylidodane) was also used as the nitrene source in the aziridination reaction, but the tosyl group proved difficult to remove from the sensitive product

later in the synthesis. When acetonitrile was used as the solvent for the aziridination reaction, the *er* decreased to 2:1. It is probable that acetonitrile competes with the bis(oxazoline) as a ligand for the copper, leading to aziridination catalysis by achiral copper complexes when acetonitrile is used as the solvent.

Initially, the aziridine was opened using catalytic TFA in MeOH, but the diastereoselectivity of ring opening was moderate (2:1). This was interpreted as meaning that the benzylic carbon-nitrogen bond was so weakened by the electron-rich nature of the phenol that ring opening was occurring by both S_N1 and S_N2 mechanisms. In an attempt to eliminate the S_N1 character of the reaction, the aziridine was subjected to ring opening in methanol that contained no acid catalyst. Under those circumstances, clean *anti* substitution was observed, leading to no loss of diastereoselectivity.

It was also observed that if the copper is not removed by filtration prior to the addition of MeOH, the *dr* decreases to 9:1. The probable explanation is that the unremoved copper acts as a Lewis acid, thereby catalyzing a non-diastereoselective, S_N1 -type ring opening of the aziridine. Our previous results with protic acids (*vide supra*) lend support to that hypothesis.

To complete the synthesis, compound **6** (Scheme 2) was treated with 4-methoxythiophenol¹⁰ and K_2CO_3 to deprotect the nosyl group, affording the free amine **7** in 90% yield, and was reprotected with an Fmoc to yield **8** in 78% yield. To confirm the configurational assignment of **8** as (2*R*,3*R*), **7** was treated with TBAF (Scheme 3) to deprotect the TBS group, yielding **10** in 68% yield. The (2*S*,3*R*) and (2*S*,3*S*) diastereomers of **10** have been previously reported in the literature,^{4b} and the NMR spectra of **10** agree with the published spectra of the (2*S*,3*S*) and not the (2*S*,3*R*) diastereomer. The specific rotation of the (2*S*,3*S*) diastereomer was reported as +42.0 (*c* 0.80, MeOH)^{4b} and the value for **10** was found to be -77.0 (*c* 0.41, MeOH), confirming the absolute configuration of **10** as (2*R*,3*R*).

In summary, we have reported an enantio- and diastereoselective synthesis of a protected form of (2*R*,3*R*)- β -methoxytyrosine. We believe that this method will prove amenable to the large-scale synthesis of the protected form of (2*R*,3*R*)- β -methoxytyrosine for our studies and others'. A protected version of the amino acid (**8**) suitable for use in solid-phase synthesis, was synthesized in four steps and 62% overall yield with a greater than 19:1 *dr* and 28:1 *er*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
(2R,3R)-β-Methoxytyrosine (1), Callipeltin A (2), Papuamides A (3) and B (4)

Scheme 1.

Scheme 2.

Scheme 3.