Pergamon

Tetrahedron Letters, Vol. 38, No. 22, pp. 3853-3856, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00770-3

Asymmetric Synthesis of Unusual Amino Acid: Synthesis of Four Isomers of β-Methyl-3-(2'-Naphthyl)alanine

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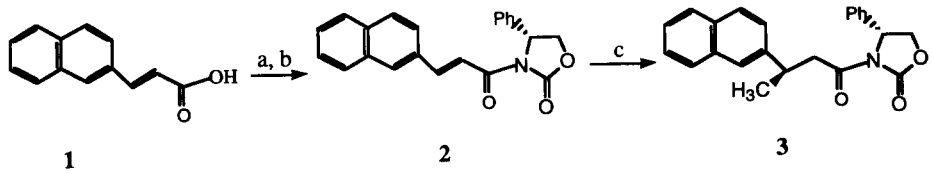
Abstract: The synthesis of all four individual isomers of 3-methyl-3-(2'-naphthyl)analine was accomplished using asymmetric conjugate 1,4-addition followed by direct or indirect azidation using an Evans-type chiral auxiliary (4-phenyl-2-oxazolidinone). © 1997 Elsevier Science Ltd.

Incorporation of β-methyl amino acids into bioactive peptides presents a rational approach to the design of highly potent and selective ligands with specific conformational and topographical features.[1] These unique features are targeted toward the design and synthesis of specific amino acids whose side-chain χ^1 and χ^2 tortional angles are significantly restricted due to steric hindrance by replacement of either the pro-R or pro-S β-hydrogens with a methyl group and other substituents. The syntheses of several β-branched α amino acids have been reported from this group, including β-methylphenylalanine,[2] β-methyltyrosine,[3] β-methyl-2', 6'-dimethyltyrosine (TMT)[4] and β-methyltryptophan.[5] As part of our investigations of rational peptide molecular design related to structure-biological activity studies, we are particularly interested in bulky aromatic amino acids as important structural surrogates of phenylalanine and tryptophan. Here we report, the stereoselective synthesis of all four individual isomers of the novel amino acid β-methyl-3-(2'-naphthyl)alanine.

The synthesis, as outlined in Scheme I, commenced with the α,β-unsaturated acid **1**, which was prepared from 2-naphthylaldehyde and triethyl phosphonoacetate *via* the Horner-Emmons olifination reaction, followed by alkaline hydrolysis (LiOH) and acidification. The coupling of the optically pure chiral auxiliary (4R)-4-phenyloxazolidinone to the acid **1** was accomplished[6] *via* the activation of the carboxylic acid either by formation of a mixed anhydride or an acyl chloride, followed by addition of lithiated oxazolidinone, to give pure N-acyloxazolidinone **2** after purification.[7] It was found that the acyl chloride method gave a higher yield.

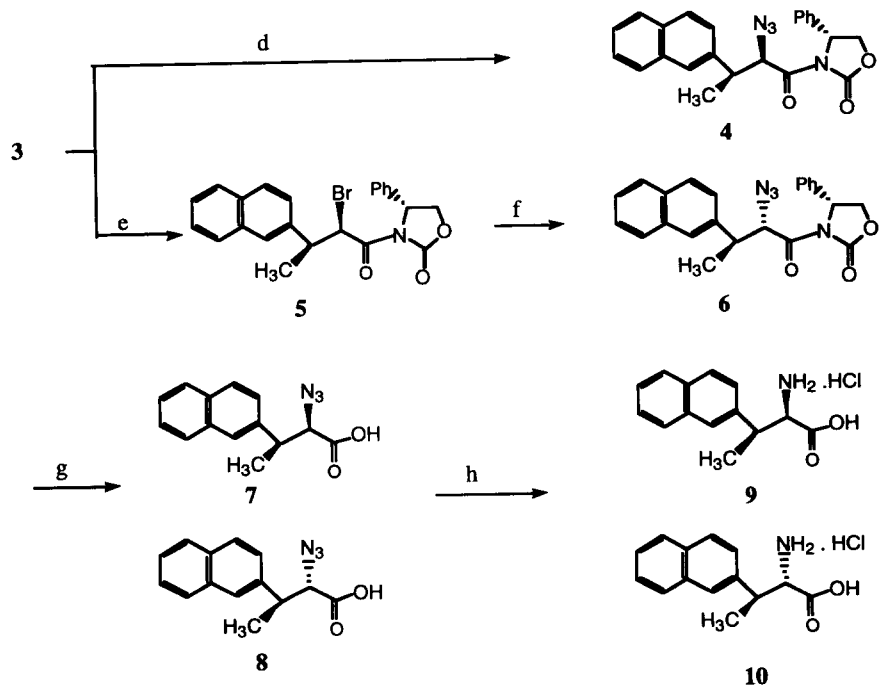
The addition of the β-methyl group was performed *via* a copper-mediated[8] asymmetric 1,4-conjugate addition. Thus, the methylcopper reagent, generated *in situ* by the treatment of methylmagnesium bromide and CuBr-dimethyl sulfide complex, was added to the acyloxazolidinones **2** to provide the methylated product **3** in

Scheme I



(a) oxalyl chloride, THF, catalytic DMF, rt, 16 h; (b) n-BuLi, (4R)-4-phenyloxazolidinone, -60 °C to rt, 3 h, 78%; (c) CH_3MgBr, CuBr-Me_2S, THF/Me_2S (1/1), -60 °C to 0 °C; 76%, >90% de;

Scheme II



(d) 1.1 eq. KHMDS, 1.2 eq. Trisyl Azide, THF, -77 °C, 94%, >95% de; (e) 1.1 eq. $(n\text{-}Bu)_2BOTf$, 1.2 eq. DIEA, -77 °C, then 1.2 eq. NBS, -77 °C, 95% (flash column, chromatograph), >95% de; (f) 1.6 eq. TMGA, AcCN, rt, 5 h, 80%, (g) 2 eq. LiOH, 4.0 eq H_2O_2, <0 °C, rt, 5 h, 92-93%; (h) H_2, 25 psi, 10% Pd/c, Ethanol, 2 eq. 6 N HCl, 2 hr, rt, 79-87%.

more than 90% diastereoisomeric excess (de). The other diastereoisomer was not detected in the crude product by ^{1}H NMR. Compound **3** was easily purified by recrystallization.[7]

The availability of **3** set the stage for the stereoselective introduction of an azide group in the α position, either directly or indirectly, yielding two diastereoisomers which eventually lead to the desired *D* and *L* amino acids (Scheme II). Direct azidation, according to the method developed by Evans *et al.*,[9] was performed by treatment of **3** with potassium hexamethyldisilazide (KHMDS) followed by trisyl azide to give the *D* azide epimer **4** in excellent yield (94% after flash column chromatography) and diastereoselectivity (>95% de). The *L* isomer **6** was prepared by the stereoselective bromination/nucleophilic azidation sequence.[9] Thus, reaction of N-bromosuccinimide (NBS) with the dibutylboryl enolate derived from **3** afforded the bromide **5**, and displacement of the bromide with nucleophilic azide (tetramethylguanidinium azide TMGA)[10] *via* an S_N2 mechanism, gave the desired *D* isomer **6**[11] with no detectable diastereoisomer. Attempts to prepare the bromide **5** from **3** using the one-pot tandem Michael-like addition/electrophilic bromination reaction[12] gave only a 62% de.

The non-destructive removal of the phenyloxazolidinone chiral auxiliary of the optically pure compounds **4** and **6** was achieved using previously published procedures,[10] providing the azido acids **7** and **8**. No racemization at the α-carbon was detected in either case. The resulting azido acids, **7** and **8**, were reduced by hydrogenation in ethanol and 2 equivalents 6 N HCl to give the corresponding amino acids **9** and **10** as their HCl salts.[13] Low hydrogen pressure (25 psi) and short reaction times (2 hr) were the preferred conditions for reduction to the amine to avoid side products.

The preparation of the other pair of diastereoisomers was achieved in the same fashion by using (4S)-4-phenyloxazolidinone as the chiral auxiliary. The unique comformational properties of these novel amino acids are under investigation.

Acknowledgments: Supported in part by grants from the US Public Health Services DK 17420 and NIDA 06284.

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11. The absolute stereochemistry at α and β carbons was confirmed by an X-ray crystal structure of the (2R, 3R) azide, the enantiomer of **6**, but the quality of the data was not suitable for publication.
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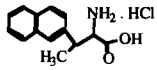
13. The final products were obtained in multi-gram quantities as white powders from ether after removal of catalyst by filtration and concentration of the filtrate. The four isomers were characterized as follows:

	HRMS (FAB) MH^+ Calcd(230.1181) Found	$[\alpha]^{22}_D$ (ETOH)	^{1}H NMR(250MHz, D_2O)	^{13}C NMR(62.9MHz, D_2O)
9 (2R, 3S)	230.1180	-30.9 (*c* 0.64)	δ1.26(d, J = 7.2 Hz, 3H), 3.45(m, 1H), 4.05(d, J = 5.6 Hz, 1H)	δ14.54, 39.68, 58.53, 171.13
10 (2S, 3S)	230.1166	+1.9 (*c* 0.52)	δ1.23(d, J = 7.1 Hz, 3H), 3.29(m, 1H), 4.0(d, J = 7.3 Hz, 1H)	δ16.74, 40.29, 58.52, 170.20
(2S, 3R)	230.1179	+30.5 (*c* 0.88)	δ1.28(d, J = 7.2 Hz, 3H), 3.48(m, 1H), 4.06(d, J = 5.7 Hz, 1H)	δ14.61, 39.72, 58.58, 171.15
(2R, 3R)	230.1174	-2.1 (*c* 0.96)	δ1.29(d, J = 7.1 Hz, 3H), 3.35(m, 1H), 3.97(d, J = 7.3 Hz, 1H)	δ16.71, 40.25, 58.50, 171.16

(*Received in USA* 10 *March* 1997; *revised* 15 *April* 1997; *accepted* 17 *April* 1997)