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Diastereospecific Tandem Michael-Like Addition / Electrophilic Bromination: A One-pot Tandem Asymmetric Synthesis of Precursors of Unusual Amino Acids

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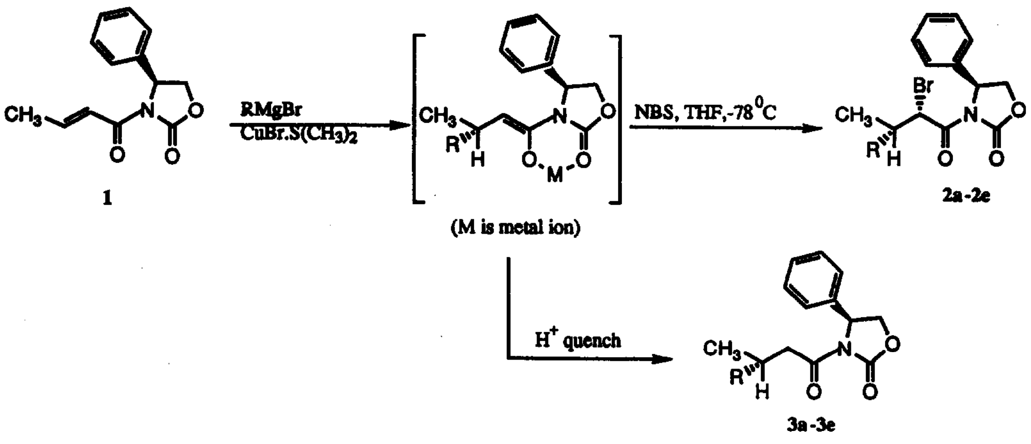
Abstract: A systematic series of key intermediates of unusual β-methyl-amino acids have been synthesized by using a modified Evans auxiliary in an asymmetric Michael-like reaction followed by direct bromination in a one-pot reaction.

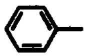
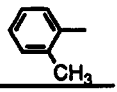
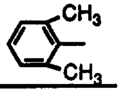
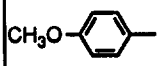
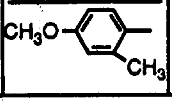
The development of novel and efficient methodology for enantioselective synthesis of α-amino acid analogues is a major objective in current organic synthesis.[1] Our major goals in this area are related to our efforts to develop a rational approach to the design of highly selective peptide and protein ligands with specific conformational and topographical features.[2] In connection with our efforts in the asymmetric synthesis of unnatural aromatic amino acids,[3] we continue to develop synthetic methods that will make these modified amino acids more accessible synthetically for use in peptide and protein design. We describe here examples of a one-pot tandem asymmetric 1, 4-conjugate addition of organocuprates to prochiral α, β-unsaturated 4-(*s*)-phenyl-*N*-crotonyl-oxazolidinone[4] **1**, followed by electrophilic bromination to furnish compounds **2a-2e**, which contain two new chiral centers in high stereoselectivities (Scheme I).

Scheme I.



A typical reaction procedure is described for example **e**. A 0 °C solution of *N*-crotonyl-oxazolinone **1**[4] (0.3 g, 1.30 mmol) in dry THF (3 mL) was added dropwise to a -78 °C preformed preparation of the organocopper reagent which resulted from copper (I) bromide-dimethyl sulfide complex (0.30 g, 1.43 mmol, 1.1 eq) and 4-methoxy-2-methylbenzylmagnesium bromide[5] (1.9 mmol, 1.1 eq, 1.3 mL of 1.47 M in THF) in THF and methyl sulfide (1:1, 5.6 mL). The resulting brown (sometimes yellow) slurry was stirred at -78 °C for 30 min, then warmed to -10 °C for 45 min. After the Michael-type addition was complete, the slurry was recooled to -78 °C and stirred for 45 min, and then transferred to a -78 °C solution of NBS (3.0 g, 3.2 eq). in THF (75 ml). The resulting mixture was stirred at -78 °C for 2 h and then at 0 °C for an additional hour. The reaction was quenched with 1.3 M sodium bisulfate (20mL) and extracted three times with EtOAc. The organic layers were washed with distilled water, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was evaluated by ^1H-NMR prior to and after silica gel chromatography (30% ethyl acetate in hexane) or recrystallization (ethyl acetate) to yield the bromide **2e** (0.43g, 80%) (Table I).

Table I.

entry	R	crude* de%	purified		$\delta_{\alpha\text{-}H}$ of bromides (ppm)	configuration	mp (°C)	$[\alpha]_D^{27}$ ($CHCl_3$)
			yield %	de %				
a		67.0	89	>99.0	5.95	(2'S, 3'S)	126-128	+35.6 (c=2.2)
b		79.0	71	>99.0	6.02	(2'S, 3'S)	176-178	+28.9 (c=2.4)
c		78.8	52	>99.0	6.47	(2'S, 3'S)	145-147	+20.9 (c=2.2)
d		83.3	55	>99.0	5.90	(2'S, 3'S)	140-144	+16.6 (c=2.2)
e		99.0 #	80	>99.0	5.98	(2'S, 3'S)@	188-191	+13.8 (c=2.8)

* Only two isomers were observed in all of the cases.

@ X-ray structure determined for (2'S, 3'S) isomer prepared from the same method[3b].

\# The best result among 20 repeated reactions

^{1}H-NMR (250 MHz) spectroscopy was convenient to monitor the reaction progress and the enantiomeric and diastereomeric selectivities for both the asymmetric Michael-like 1,4-conjugate addition intermediates **3a-3e**, and the final α-bromides **2a-2e** respectively. The absolute stereochemistry was established unequivocally by the X-ray structure determination of an (2'R, 3'S) analogue prepared by the same method,[3b] and by characterization of the optically pure azide from the displacement of **2a** (optical rotation, NMR, mp) compared to an authentic sample prepared by a different method.[6] The Michael-like addition occurred only by C_α Si-face attack on the S-*cis* conformer of the organocuprate complexes[7] **1a-e** with ee % greater than 99 % and the indicated de% of crude products **2a-2e** (Table I). Similarly *N*-crotonyloxazolidinones of opposite chirality underwent C_α Re-face attack as a consequence of the directing effect of the C-4 phenyl group in the chiral auxiliary.[3b] It is interesting to note the overall *syn*-addition following the tandem NBS reaction where the facial selectivity is controlled by the chiral auxillary, but in similar cases where no chiral auxillary is present overall *anti*-addition generally occurs and electrophilic attacking is directed by the 1, 4-Michael adduct.[8] The downfield chemical shifts of the α-methine proton of the bromides **2d-2e** (doublets) range from 5.9 to 6.47 ppm, and these could be used to evaluate the stereoselectivities after the bromination reaction. The minor diastereomeric isomers were readily separated by silica gel chromatography and recrystallization.

In summary, we have demonstrated the utility and efficiency of double asymmetric one-pot tandem Michael-like addition / electrophilic bromination reactions for the synthesis of precursors of unusual amino acids in moderate to high yields. These precursors and can be elaborated readily to their respective amino acids[3,4,6] and these will be employed in the rational design of peptide ligands.

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