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Highly Diastereoselective 1,4-Addition of Amines to Chiral α,β-Unsaturated δ-Lactone

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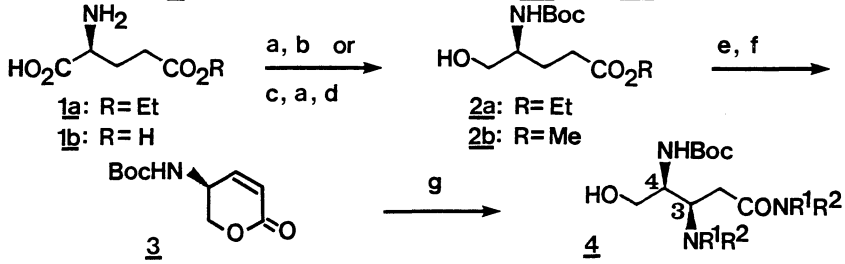
Michael addition of amines to (S)-γ-amino-α,β-unsaturated δ-lactone was accomplished in extremely high diastereoselectivity with the ring-opening reactions and was disclosed to furnish (3R,4S)-diamino-hydroxyamides in high yields.

For the design and synthesis of naturally occurring compounds possessing a wide range of biological activity, remarkable utilization of α-amino acids as chiral sources has been receiving interest.[1] Particularly, because of its versatility and commercial availability, a large number of papers using proteogenic L-glutamic acid for synthetic manipulations have appeared and indicated to afford pharmacologically potent substances.[2] In a recent continuation of our work to extend the new employment of L-glutamic acid, we have revealed efficient synthetic methods for the synthesis of natural products using stereoselective conjugate addition of organometallic reagents.[3] In this communication we wish to demonstrate that asymmetric Michael addition of suitable amines[4] to chiral unsaturated δ-lactone (3) proceeds cleanly with almost complete diastereofacial selection to provide optically active β,γ-diamino acid derivatives (4) and the absolute configuration of the newly created chiral center is established.

Chiral lactone (3) was prepared from 1a or 1b as shown in Scheme 1.[3a]



3 4

Scheme 1. Reagents and conditions: a) $(Boc)_2O$, $NaHCO_3$, H_2O; b) B_2H_6, THF; 66% (from 1a); c) TsOH, MeOH-Benzene, reflux; d) $NaBH_4$, MeOH; 62%(from 1b); e) TsOH or CSA, Benzene, reflux; 64%; f) LDA, PhSeCl, THF-HMPA,-78 °C and then MCPBA, CH_2Cl_2, -78 °C; 70%; g) Amine; see Table 1.

Then, conjugate addition of various amines to 3 was examined. As summarized in Table 1, not only primary but also secondary amines indeed underwent extremely high diastereoselective reactions in DMF or CH_2Cl_2 at low temperatures to yield (3R,4S)-diamino-amides (4)[5] exclusively. Apparently these reactions occur with the formation of the conjugate adducts at the less hindered side followed by the ring openings.[6] Since the products thus obtained correspond to the chiral β,γ-diamino acids, those would become valuable intermediates for the synthesis of biologically active compounds such as antibacterial lysobactin.

Table 1. Conjugate Addition of Amines to Chiral α,β-Unsaturated lactone (3)

Entry	Amine R^1	Amine R^2	Solvent	Temp/°C (Time/h)	b) Yield of 4 /%	c) [R,S]:[S,S]
1	H	$C_6H_5CH_2$	DMF	-78--20(3.0)	97(4a)	97: 3
2	H	$C_6H_5CH_2$	CH_2Cl_2	-78--20(3.5)	91(4a)	97: 3
3	H	$CH_3(CH_2)_3$	DMF	-78--30(2.5)	80(4b)	>99: 1
4	H	$CH_3(CH_2)_3$	DMF	-20 (2.5)	71(4b)	92: 8
5	CH_3	CH_3	CH_2Cl_2	-78 (1.0)	98(4c)	87:13
6	$-(CH_2)_4-$		CH_2Cl_2	-78 (1.0)	53(4d)	99: 1
7	$-(CH_2)_5-$		CH_2Cl_2	-78--20(4.0)	99(4e)	>99: 1
8	$-(CH_2)_5-$		CH_2Cl_2	-20 (0.5)	94(4e)	96: 4
9	$-(CH_2)_2O(CH_2)_2-$		DMF	-40--30(2.5)	58(4f)	>99: 1
10	$-(CH_2)_2O(CH_2)_2-$		CH_2Cl_2	-40--30(2.5)	73(4f)	>99: 1

a) 2-5 equiv. of reagents was used. b) Isolated yield. c) Determined by ^{13}C NMR and HPLC (Cosmosil 5PYE and $5C_{18}$ columns) analyses.

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References

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2) For example see: P. Yadagiri, S. Lumin, and J. R. Falck, Tetrahedron Lett., 30, 429(1989); M. Yanagida, K. Hashimoto, M. Ishida, H. Shinozaki, and H. Shirahama, ibid., 30, 3799(1989); F. J. Sardina, M. H. Howard, M. Morningstar, and H. Rapoport, J. Org. Chem. 55, 5025(1990).
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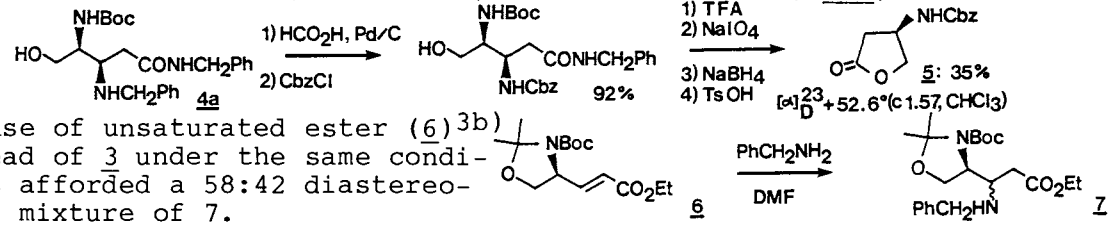
4) Recently 1,4-additions of amines to butenolides were demonstrated: B. de Lange, F. van Bolhuis, and B. L. Feringa, Tetrahedron, 45, 6799(1989).
5) In order to assign the absolute configuration, 4a was converted to known 5 according to our reported method:[3] G. J. McGarvey, J. M. Williams, R. N. Hiner, Y. Matsubara, and T. Oh, J. Am. Chem. Soc., 108, 4943(1986).



6) The use of unsaturated ester (6)[3b] instead of 3 under the same conditions afforded a 58:42 diastereomeric mixture of 7.

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