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Synthesis of Novel β-Amino Acid Precursors: β-Amino-Hydrocoumarins as Unusual Aspartic Acid Mimetics used in Fibrinogen Receptor Antagonists

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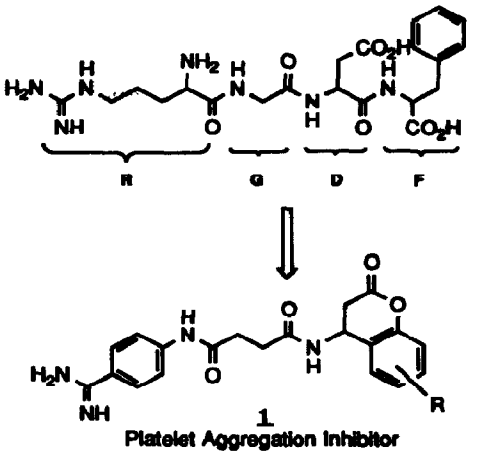
Abstract: An efficient synthesis of new β-amino-hydrocoumarins is presented. The key reaction is a Michael addition between commercially available coumarins and lithium-bis(trimethylsilyl)amide at low temperature. The trimethylsilyl groups are removed using dry HCl/dioxane to give the β-amino-hydrocoumarins as their hydrochloride salts. These conditions allow multigram scale preparations of unique β-amino lactones.

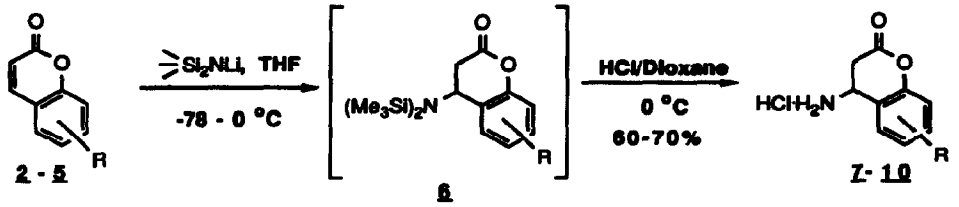
Syntheses of β-amino acids and esters have been receiving considerable attention recently because of their importance in biological systems.[1] This report describes a highly efficient procedure for the synthesis of β-amino lactones derived from readily available coumarins.

Beta amino acids are an integral component of platelet aggregation inhibitors.[2(a)] Fibrinogen binding to platelets is important for normal platelet function in the blood coagulation mechanism. Interaction of fibrinogen with platelets occurs through the membrane bound glycoprotein complex, gp IIb/IIIa; this is an important feature of the platelet function. Inhibitors of this interaction are useful in modulating platelet thrombus formation. The tetrapeptide sequence RGDF is the critical peptide sequence recognized within fibrinogen during coagulation.



1
Platelet Aggregation Inhibitor

The synthetic β-amino acids derived from β-amino lactone 1 presummably mimic the aspartic acid (D) moiety in the RGDF sequence of fibrinogen. The RGDF peptidomimetics are potent platelet aggregation inhibitors.[2 (c)] Platelet aggregation inhibitors incorporating compounds 7-10 are unique, in that they are the first reported β-amino-hydrocoumarins which function as prodrugs of the active agent.[2] To the best of our knowledge this is the first direct synthesis of β-amino lactones from coumarins.[3]



2 - 5 6 7- 10

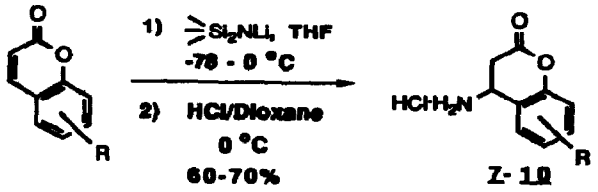
It has been demonstrated that lithium diisopropylamide undergoes congugate addition with acrylic esters.[4] Recent work from this and other laboratories shows that chiral dialkylamines can add to α,β-unsaturated esters with asymmetric induction.[2,5]

I now wish to report that the addition of lithium-bis(trimethylsilyl)amide to coumarins (2-5) gives novel β-amino lactonesthat are useful as aspartate mimics. There are two key features of significant consequence for the conjugate addition between lithium-bis(trimethylsilyl)amide and coumarins to give β-bis(trimethylsilyl)amino-hydrocoumarins (6). First, the conjugate addition proceeds smoothly at low temperature to give β-bis(trimethylsilyl)amino-hydrocoumarins, which are stable for 4-5 hours in the refrigerator. Secondly, the removal of the bis(trimethylsilyl) group is easily performed under relatively mild conditions. A typical hydrolysis protocol, such as aqueous mineral acid, resulted in polymerization of the amino-hydrocoumarins. After considerable experimentation, the only successful procedure for removal of the β-bis(trimethylsilyl) groups was addition of 4M HCl in dioxane to the β-bis(trimethylsilyl)amino-hydrocoumarin at 0 °C. An advantage of this procedure is that the β-amino-hydrocoumarin hydrochloride salts separate cleanly out of solution, thus avoiding an additional purification step by chromatography or distillation. In summary, this procedure provides efficient access to multigram scale preparations of this unique class of β-amino lactones.

General preparation of β-Amino-Hydrocoumarins:

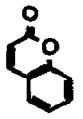
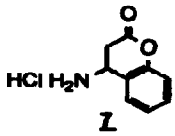
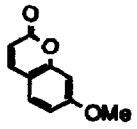
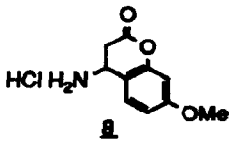
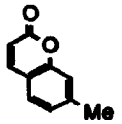
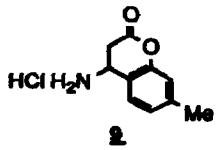
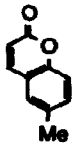
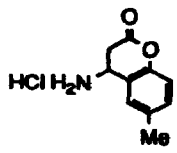
To coumarin (10 g, 68 mmol) in THF (25 ml) was added lithium bis(trimethylsilyl)amide in hexanes (70 ml, 70 mmol) and THF (75 ml) at -78 °C. After the addition, the dry ice bath was replaced with an ice bath and the course of the reaction was monitored by tlc (EtOAc/Hex). After complete reaction (30 min) ether (100 ml) was added, followed by water (100 ml). The organic layer was separated and dried over Na_2SO_4. The solvent was removed to leave crude β-N-bis(trimethylsilyl) lactone. To this amber oil was added ethyl acetate (100 ml) and the solution cooled to 0 °C. Dry hydrochloric acid in dioxane (4N,20 ml) was added. The product was filtered, and washed with ether to give of β-amino lactone hydrochloride 7 (6.6 g, 70%).[6]

All β–amino-hydrocoumarins are stable as their hydrochloride salt and can be stored at room temperature without decomposition. Furthermore, all the β–amino-hydrocoumarins undergo smooth reaction with activated carboxylic acids when neutralized in solution.[2(a)]



Z- 10

Table 1

Entry	Coumarin	β-Amino-Hydrocoumarin	%Yield
2		 Z	70
3		 8	60
4		 9	62
5		 10	69

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1. (a) Konopelski, J.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**,*56*, 1355-1357. (b) Bovy, P. R.; McMackins, D. E.; Rico, J. G.; Tjoeng, F. S.; Toth, M. V.; Garland, R. B.; Miyano, M.; Zablocki, J. A.; US Patent number 5,220,050, **1993**; Bovy, P. R.; Rico, J. G.; Rogers, T. E.; Tjoeng, F. S.; Zablocki, J. A.; US Patent number 5,239,113, **1993**. (c) For a review: Barret, G. C. (Ed.), Beta and Higher Homologous Amino Acids in *Chemistry and Biochemistry of the Amino Acids*, Chapman and Hall, New York, 1985, pp. 25-54. (d) A recent review of β-amino acids: Juarista, E., Quintana, D., Escalante, J.; *Aldrichimica Acta*, **1994**, *27*, 3-11.
2. (a) RGDF Peptidomimetics were prepared according to: Rico, J. G.; Lindmark, R. J.; Rogers, T. E.; Bovy, P. R. *J. Org. Chem.* **1993**, *58*, 7948-7951, and references cited therein (b) For a recent synthesis of a β-amino acid see: Bovy, P. R.; Rico, J. G.; *Tetrahedron Lett.* **1993**, *34*, 8015-8018 (c) The active agent is the open form of the β-amino lactone.
3. A report on synthesis of a β-amino-γ-butyrolactone: Hvidt, T.; Szarek, W. A.; McClean, D. B. *Can. J. Chem.* **1988**, *66*, 779-782. A report on synthesis of a β-amino-γ-butyrolactam: Ede, N. J.; Rae I. D.; Hearn, M. T. W.; *Tetrahedron Lett.* **1990**, *31*, 6071-6074.
4. Herrman, J. L.; Kleczykowski, G. R.; Schlessinger, R. H.; *Tetrahedron Lett.* **1973**, 26, 2433-2436.
5. Davies, S. G.; Ichihara, O.; *Tetrahedron Asymmetry* **1991**, *2*, 83-186. Also Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S.; *Tetrahedron Lett.* **1985**, *26*, 4133-4136.
6. A typical NMR spectrum for β-amino-hydrocoumarins follows: All new compounds showed satisfactory NMR, mass spectral and elemental analyses.

   Compound 7. ^{1}H NMR, (300 MHz d_6-DMSO), δ, 2.8 (m, 2H), 4.9 (m,1H), 7.2-7.7 (m, 4H), 9.1 (bs, 3H).; FABMS (M+H) 164.3.

   Compound 8. ^{1}H NMR, (300 MHz d_6-DMSO), δ, 2.3 (s, 3H), 2.9 (m, 2H), 4.8 (bs,1H), 7.2-7.5 (m, 3H), 9.0 (bs, 3H).; FABMS (M+H)194.1.

   Compound 9. ^{1}H NMR, (300 MHz d_6-DMSO), δ, 2.4 (m, 2H), 2.8 (s, 3H), 4.7 (bs,1H), 7.1-7.5 (m, 3H), 9.2 (bs, 3H).; FABMS (M+H) 178.2.

   Compound 10. ^{1}H NMR, (300 MHz d_6-DMSO), δ, 3.05 (m, 2H), 3.8 (s, 3H), 4.9 (bs,1H), 7.4-7.7 (m, 3H), 8.9 (bs, 3H).; FABMS (M+H) 178.1.

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