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Enantiospecific Synthesis of SB 214857, a Potent, Orally Active, Nonpeptide Fibrinogen Receptor Antagonist

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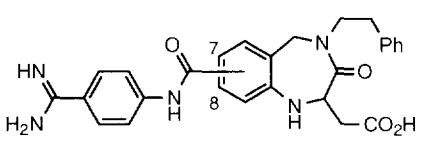
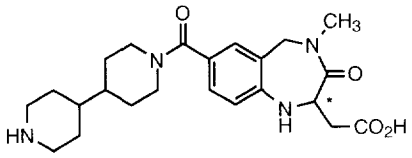
Abstract: An enantiospecific synthesis of SB 214857, a potent, nonpeptide fibrinogen receptor antagonist, is reported. The synthetic route employs as a key step an intramolecular aryl fluoride displacement to form the seven-membered ring of the 1,4-benzodiazepine system.

Recently, we reported[1] the direct design of 1,4-benzodiazepine **1** from a constrained peptide, and showed **1** to be a highly potent and selective fibrinogen receptor antagonist.[2] In a continuation of our preliminary studies,[3] we moved the point of attachment of the amidinophenyl side chain from the 8-position to the 7-position to afford **2**. Although **2** was somewhat less active than **1** in both binding affinity and antiaggregatory potency,[3] subsequent SAR studies led to the identification of SB 214134 (**3**) as a highly potent, selective, and orally active fibrinogen receptor antagonist.[4] Further investigation revealed that the biological activity of **3** resided exclusively in the (-)-enantiomer, SB 214857 (**4**). However, since the individual enantiomers of **3** were originally obtained via a preparative chiral HPLC separation of a late-stage racemic intermediate, the absolute configuration of **4** remained uncertain. In order to address this issue, and to be able to provide a large quantity of SB 214857 for additional studies, we required an efficient and enantiomerically unambiguous synthesis. In this report, we describe an enantiospecific synthesis of SB 214857 from a derivative of L-aspartic acid, which allowed us to definitively assign the absolute configuration of the asymmetric center, and additionally provided access to multigram quantities of material for additional biological testing.



1 8-substitution
2 7-substitution



3 racemic (SB 214134)
4 (-)-enantiomer (SB 214857)

Our strategy for the synthesis of SB 214857 was to employ an intramolecular displacement of an activated aryl halide to construct the seven-membered ring of the 1,4-benzodiazepine system (Scheme 1). A

similar strategy has been used in the construction of related 1,4-benzodiazepine systems,[5] and we had previously demonstrated the feasibility of the cyclization of **5** to **6** wherein the halide was either chloride or fluoride (X = Cl or F) and the activating group was a nitro group (Z = NO_2).[6] In extending these studies to SB 214857, we would require a carboxylic ester (Z = CO_2R^3) or related group (carboxylic acid or amide) as the activating group, which is much less electron withdrawing than a nitro group. Thus, the successful implementation of this strategy in the synthesis of SB 214857 depended on whether a carboxylic ester (or related group) would be sufficiently activating to allow for displacement of the aryl halide, and on whether the cyclization would proceed without racemization.

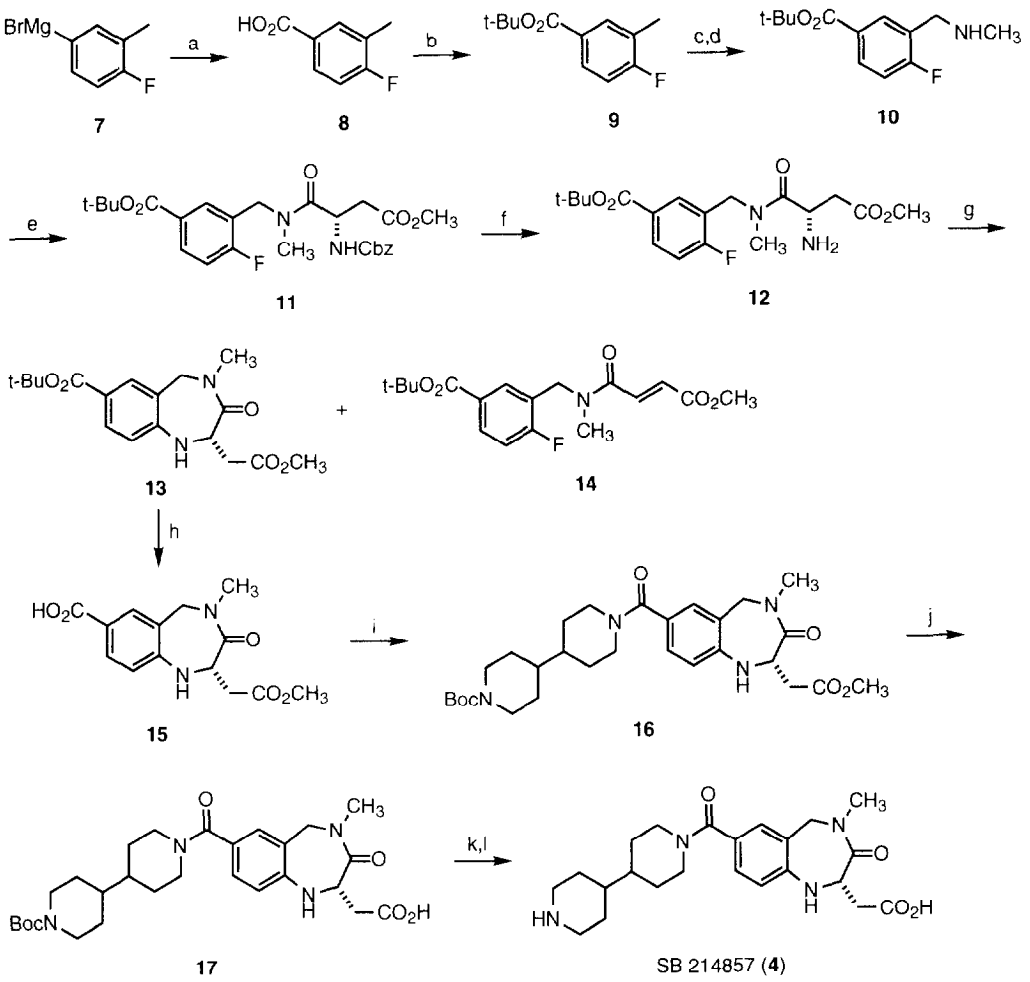
Scheme 1

5 **6**

The synthesis of SB 214857 is illustrated in Scheme 2. Carboxylation of commercially available 4-fluoro-3-methylphenylmagnesium bromide (**7**) in THF afforded a 77% yield of 4-fluoro-3-methylbenzoic acid (**8**),[7] which was esterified with isobutylene in the presence of catalytic trifluoromethanesulfonic acid to give *tert*-butyl ester **9** in 94% yield. Benzylic bromination with NBS, followed by reaction of the crude benzyl bromide with excess 40% aqueous methylamine in THF, gave amine **10** in 70% overall yield from **9**. The amino group in **10** was acylated with N-Cbz-L-aspartic acid β-methyl ester[8] in the presence of DCC and HOBt to afford amide **11** in 86% yield. Hydrogenolysis of the Cbz protecting group in **11** under standard conditions gave cyclization precursor **12** in 98% yield. When a 0.1 M solution of **12** in anhydrous DMSO was warmed for 18 hours in an oil bath preset at 125°C, **12** was completely consumed and the desired cyclization product **13** was obtained in 47% yield, together with a 28% yield of the elimination product **14**. Attempts to minimize the formation of **14** are under investigation.[9] Analysis of **13**, $[\alpha]_D$ -262.1° (*c* = 1.0, MeOH), by chiral HPLC[10] revealed an *S:R* ratio of >99:1, confirming that the cyclization had indeed proceeded without racemization.[11]

To complete the synthesis, the *tert*-butyl ester of **13** was deprotected with trifluoroacetic acid in CH_2Cl_2 in the presence of anisole to afford carboxylic acid **15** in 95% yield. Coupling of **15** with 1-Boc-4,4'-bipiperidine[6] in the presence of EDC afforded fully protected SB 214857 (**16**) in 94% yield. Saponification to afford carboxylic acid **17**, followed by removal of the Boc protecting group and purification, afforded zwitterionic SB 214857 (**4**), $[\alpha]_D$ -200.1° (*c* = 0.5, MeOH), in good overall yield. Analysis of totally synthetic SB 214857 by chiral HPLC[10] showed an *S:R* ratio of >99:1, and biological assay[4] confirmed that we had prepared the biologically active enantiomer of SB 214134 (**3**). Full details of the biological evaluation of SB 214857 will be published elsewhere.[4]

Scheme 2



a) CO_2, THF (77%); b) isobutylene, 5 mole % TfOH, Et_2O, sealed pressure bottle, -78°C to RT (94%); c) NBS, $(PhCO)_2O_2$, CCl_4, reflux; d) 40% aq. CH_3NH_2, THF (70% from **9**); e) Cbz-L-Asp-β-methyl ester, DCC, HOBt·H_2O, DMF (86%); f) H_2, 10% Pd/C, MeOH (98%); g) 0.1 M **12** in anhydrous DMSO, 125°C (bath temperature) (47% of **13**, 28% of **14**); h) 1:1 TFA/CH_2Cl_2, anisole (95%); i) 1-Boc-4,4'-bipiperidine, EDC, $(i\text{-}Pr)_2NEt$, DMF (94%); j) 2.0 N NaOH (2 eq.), 1:1 MeOH/THF, then AcOH (81%); k) 4 M HCl in dioxane, $CHCl_3$, then neutralization of excess reagent with ca. 1.0 N KOH in EtOH to give **4** · HCl (75%); l) precipitation from aqueous solution at pH 6.8 (83%).

In summary, we have synthesized enantiomerically pure SB 214857 (**4**) from a derivative of L-aspartic acid. The synthetic route incorporates as a key operation an intramolecular displacement of an activated aryl fluoride to construct the seven-membered ring of the 1,4-benzodiazepine system, and thereby establishes that a carboxylic ester is in fact sufficiently activating to allow for such a reaction in the intramolecular sense. Further, the cyclization proceeded without racemization, and thus the absolute configuration of the single

asymmetric center of SB 214857 is established as (*S*). Finally, the synthesis has been scaled up to provide multigram quantities of SB 214857 for biological testing.

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References and notes

1. Ku, T. W.; Ali, F. E.; Barton, L. S.; Bean, J. W.; Bondinell, W. E.; Burgess, J. L.; Callahan, J. F.; Calvo, R. R.; Chen, L.; Eggleston, D. S.; Gleason, J. G.; Huffman, W. F.; Hwang, S.-M.; Jakas, D. R.; Karash, C. B.; Keenan, R. M.; Kopple, K. D.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M. F.; Peishoff, C. E.; Samanen, J. M.; Uzinskas, I.; Venslavsky, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 8861 - 8862.

2. For recent reviews on fibrinogen receptor antagonists, see a) Nichols, A. J.; Vasko, J. A.; Koster, P. F.; Valocik, R. E.; Samanen, J. M. in *Cellular Adhesion: Molecular Definition to Therapeutic Potential;* Metcalf, B. W., Dalton, B. J., Poste, G., Eds.; Plenum Press: New York, 1994; p. 213 - 237. b) Cook, N. S.; Kottirsch, G.; Zerwes, H.-G. *Drugs of the Future* **1994**, *19*, 135 - 159. c) Blackburn, B. R.; Gadek, T. R. *Ann. Rep. Med. Chem.* **1993**, *28*, 79 - 88. d) Nichols, A. J.; Ruffolo, R. R., Jr.; Huffman, W. F.; Poste, G.; Samanen, J. *Trends in Pharmaceutical Sciences* **1992**, *13*, 413 - 417.

3. Ku, T. W.; Miller, W. H.; Bondinell, W. E.; Erhard, K. F.; Keenan, R. M.; Nichols, A. J.; Peishoff, C. E.; Samanen, J. M.; Wong, A. S.; Huffman, W. F. *J. Med. Chem.* **1995**, *38*, 9 - 12.

4. Samanen, J.; Ali, F. E.; Barton, L.; Bondinell, W.; Burgess, J.; Callahan, J.; Calvo, R.; Chen, L.; Chen, K.; Erhard, K.; Heyes, R.; Hwang, S.-M.; Jakas, D.; Keenan, R.; Ku, T.; Kwon, C.; Lee, C.-P.; Miller, W.; Newlander, K.; Nichols, A.; Peishoff, C.; Rhodes, G.; Ross, S.; Shu, A.; Simpson, R.; Takata, D.; Yellin, T. O.; Uzinskas, I.; Venslavsky, J.; Wong, A.; Yuan, C.-K.; Huffman, W. In *The Proceedings of the 14th American Peptide Symposium (Peptides: Chemistry, Structure and Biology);* Kaumaya, P. T. P., Hodges, R. S., Eds.; Escom: Leiden, The Netherlands, 1995; In Press.

5. a) De Knaep, A. G. M.; Moens, L. J. R.; Vreysen, E. J. C. PCT Int. Appl. WO 9306106 (1 Apr. 1993). b) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1992**, *57*, 97-100. c) Parker, K. A.; Coburn, C. A. *J. Org. Chem.* **1991**, *56*, 4600-4601.

6. Bondinell, W. E.; Callahan, J. F.; Huffman, W. F.; Keenan, R. M.; Ku, T. W.; Newlander, K. A.; Samanen, J. M.; Uzinskas, I. N. WO 9414776 (7 July 1994).

7. All new compounds gave satisfactory spectroscopic and analytical data.

8. Goodman, M.; Boardman, F. *J. Am. Chem. Soc.* **1963**, *85*, 2483-2490.

9. Interestingly, attempts to use a disubstituted amide as the activating group, or to effect the intermolecular addition of L-Asp dimethyl ester to *tert*-butyl 4-fluorobenzoate, were unsuccessful.

10. Chiral HPLC conditions: For compound **13**: CHIRALCEL OD-R®; 4.6 x 250 mm; 75% CH_3OH/25% H_2O; 0.6 mL/min; UV detection at 254 nM; t_R (*R*) = 18.2 min; t_R (*S*) = 20.6 min. For SB 214857 (**4**): CYCLOBOND I 2000 SP®; 4.6 x 250 mm; 10% CH_3CN/90% aqueous triethylammonium acetate (0.17 M, pH 4.5); 1.0 mL/min; UV detection at 254 nM; t_R (*R*) = 11.3 min; t_R (*S*) = 13.6 min.

11. The synthesis was repeated using Cbz-D-Asp β-methyl ester to provide ent-**13**, $[\alpha]_D$ +267.6° (*c* = 1.0, MeOH), with an *R*:*S* ratio of >99:1 by chiral HPLC.[10]

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