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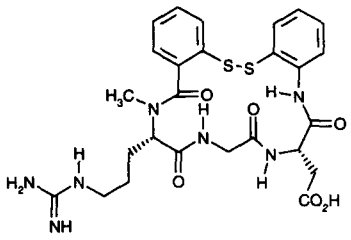
An Alternate Enantiospecific Synthesis of Methyl (S)-7-tert-Butoxycarbonyl-2,3,4,5-Tetrahydro-4-Methyl-3-Oxo-1H-1,4-Benzodiazepine-2-Acetate

Thomas W. Ku, * Fadia E. Ali, William E. Bondinell, Karl F. Erhard, William F. Huffman, Joseph W. Venslavsky, and Catherine C.-K. Yuan

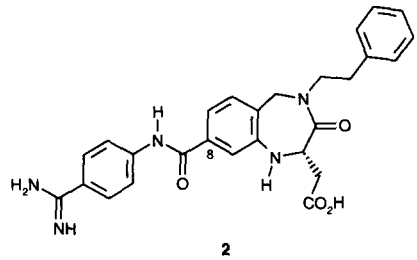
Department of Medicinal Chemistry, Research and Development Division, SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939 USA

Abstract: An alternate enantiospecific synthesis of methyl (S)-7-tert-butoxycarbonyl-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (**5**) is reported. The key step, which involves an intermolecular displacement of the activated aryl fluoride (**9**) by L-aspartic acid β-methyl ester, proceeds without racemization. © 1997 Elsevier Science Ltd.

Platelet activation, adhesion, and subsequent aggregation have been shown to play a critical role in various thrombogenic disorders. [1-3] The binding of the dimeric plasma protein fibrinogen to GPIIb/IIIa receptors [4,5] on the surface of adjacent activated platelets is the final, common pathway in platelet aggregation, independent of stimuli. Disruption of this crosslinking process mediated in part by the Arg-Gly-Asp (RGD) sequences may provide a new therapeutic approach for the treatment and prevention of acute myocardial infarction, unstable angina or thrombotic stroke. [6,7]



1 (SK&F 107260)



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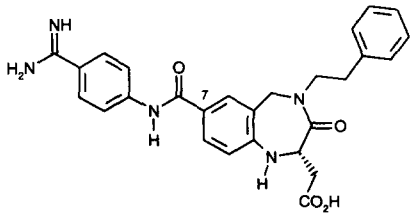

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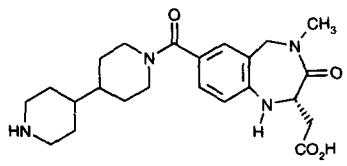
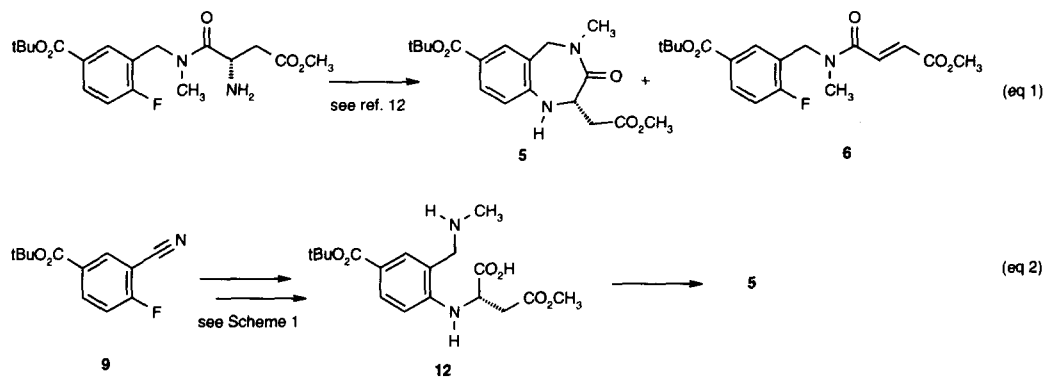


4 (SB 214857)

We have previously reported the direct design and synthesis of the highly potent and selective non-peptide fibrinogen receptor antagonist **2**,[8] based on the turn-extended-turn structural motif of the constrained Arg-Gly-Asp-containing cyclic semipeptide **1**.[9] We then moved the amidinophenyl side chain from the 8-



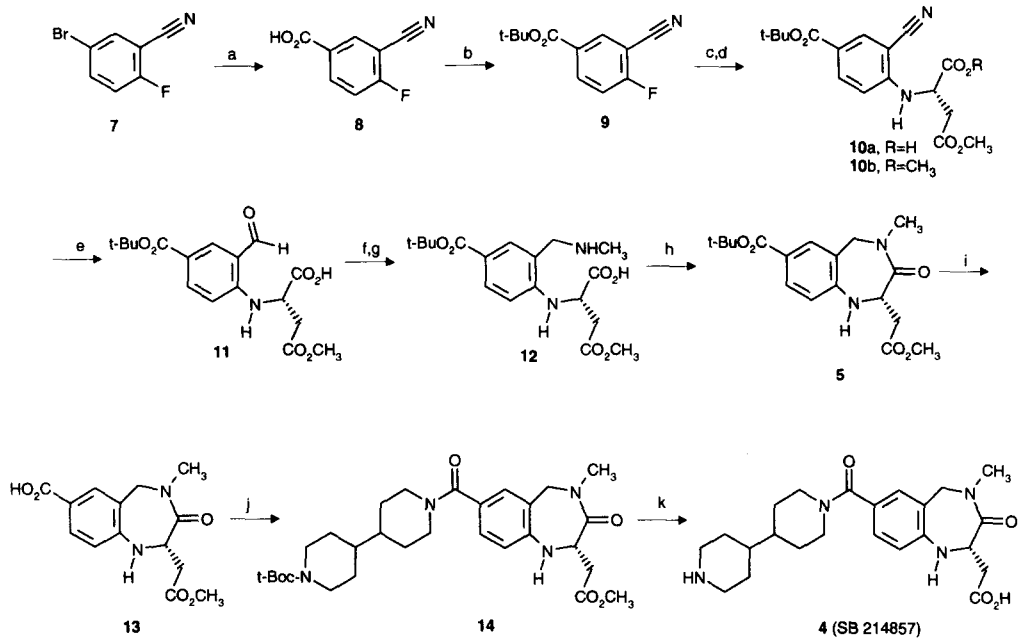
position to the 7-position to afford the slightly less potent compound **3**,[10] which led to the identification of SB 214857 (**4**) as a highly potent, selective, and orally active fibrinogen receptor antagonist.[11,12] Our previously reported enantiospecific synthesis of **4** relied on an intramolecular aryl fluoride displacement to give the benzodiazepine template **5** [13]. Unfortunately, this cyclization reaction was accompanied by an unacceptable level of β-elimination to give the fumarate by-product **6** (eq 1). To avoid fumarate formation, we investigated the ring cyclizaton and the fluoride displacement reactions in the reversed order (eq 2). We herein report this alternate enantiospecific synthesis of methyl (S)-7-tert-butoxycarbonyl-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (**5**) starting from commercially available 5-bromo-2-fluorobenzonitrile (**7**) and L-aspartic acid β-methyl ester (Scheme 1).

Palladium-catalyzed carboxylation of 5-bromo-2-fluorobenzonitrile (**7**) with carbon monoxide in the presence of potassium acetate afforded 3-cyano-4-fluorobenzoic acid (**8**)[14] in 52% yield. Subsequent esterification with isobutylene and triflic acid in diethyl ether gave *tert*-butyl ester **9** in 72% yield. A suspension of **9**, L-aspartic acid β-methyl ester, and sodium bicarbonate in aqueous DMSO was heated at 72 °C for 24 hr to yield the desired displacement product **10a** in 75% isolated yield. Esterification of **10a** in the presence of methanol and BOP reagent gave N-(aryl)aspartic acid dimethyl ester **10b** in 70% yield. Chiral HPLC [15] analysis showed that **10b** had an *S:R* ratio of >99:1, confirming that the arylfluoride displacement proceeded without racemization. The success of the aryl fluoride displacement reaction appears to depend on two critical factors. Previously, we reported our unsuccessful attempts to effect an intermolecular addition of L-Asp dimethyl ester to *tert*-butyl 4-fluorobenzoate. [12] However, *tert*-butyl 3-cyano-4-fluorobenzoate **9** undergoes a facile displacement to afford **10a**. Thus, incorporation of the electron withdrawing nitrile group into the fluoroaromatic substrate appears to facilitate the intermolecular displacement. Secondly, when the aryl fluoride displacement reaction was attempted using L-Asp dimethyl ester, the product **10b** was found to be racemic. This result suggests that the carboxylate salt of L-Asp β-methyl ester formed under the reaction conditions protects the amino acid from racemization.

Reductive hydrolysis of **10a** in warm pyridine/acetic acid/water with Raney-nickel afforded benzaldehyde **11** in 84% yield. Reductive amination of **11**, followed by cyclizaton of the resulting benzylamino acid **12** in the presence of BOP reagent and triethylamine afforded the desired benzodiazepine **5** in 25% overall yield from **11** [16]. Analysis by chiral HPLC [15] revealed that **5**, $[\alpha]_D$ -261.2° (*c* = 1.0, MeOH),

{lit. [12] $[\alpha]_D$ -262.1° (c = 1.0, MeOH)}, had an *S:R* ratio of >99:1, confirming that elaboration of the nitrile to the amino acid precursor and the subsequent cyclization had proceeded without racemization. **5** was converted to carboxylic acid **13** in high yield, which was coupled with 1- Boc-4,4'-bipiperidine in the presence of EDC and HOBt to give **14** in 59% yield by a previously reported procedure. [13b] Analysis by chiral HPLC [15] showed that **14**, $[\alpha]_D$ -139.3° (c = 1.0, MeOH), had an *S:R* ratio of >99:1.

Scheme 1



a) CO, dppf, $Pd(OAc)_2$, KOAc, DMSO (52%); b) isobutylene, 5 mole % TfOH, Et_2O, sealed pressure bottle, -78°C to RT (72%); c) L-Asp-β-methyl ester, DMSO, $NaHCO_3$, 72°C (75%); d) CH_3OH, BOP reagent, Et_3N (70%) ; e) pyridine, HOAc, H_2O, H_2, Raney/Ni, 60°C (84%); f) CH_3NH_2, EtOAc, $MgSO_4$; g) HOAc, PtO_2, H_2; h) BOP reagent, Et_3N (25% from **11**); i) 1:1 TFA/CH_2Cl_2 (90%); j) 1-Boc-4,4'-bipiperidine, EDC, HOBt, $(i\text{-}Pr)_2NEt$, DMF (59%); k) see ref 12.

In summary, we have synthesized enantiomerically pure methyl (S)-7-tert-butoxycarbonyl-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (**5**) from commercially available L-aspartic acid β-methyl ester. We have shown that the intermolecular displacement of the activated aryl fluoride with commercially available L-aspartic acid β-methyl ester proceeded without racemization or β-elimination. Further elaboration of the nitrile to the amino acid precursor and the subsequent cyclization to give the 1,4-benzodiazepine ring system also proceeded without any loss of stereochemical integrity.

Acknowledgments. We thank the Department of Physical and Structural Chemistry for mass spectral support and Ms. Edith A. Reich of the Department of Physical and Structural Chemistry for elemental analysis.

References and notes

1. Coller, B. S. *N. Engl. J. Med.* **1990**, 322, 33-42.
2. Phillips, D. R.; Charo, I. F.; Parise, L. V.; Fitzgerald, L. A. *Blood* **1988**, *71*, 831-843.
3. Pierschbacher, M. D.; Ruoslahti, E. *Nature* **1984**, *309*, 30-33.
4. Plow, E. F.; Ginsberg, M.; Marguerie, G. A. In *Biochemistry of Platelets*; D. R. Phillips and M. R. Shuman, Ed.; Academic Press: New York, **1986**; pp 226-251.
5. Gartner, T. K.; Bennett, J. S. *J. Biol. Chem.* **1985**, *260*, 11891-11894.
6. Strony, J.; Adelman, B.; Phillips, D. R.; Scarborough, R. M.; Charo, I. F. *Circulation* **1991**, *84* (October Suppl.), 0985a.
7. For recent reviews on fibrinogen receptor antagonists, see a) Samanen, J. *Ann. Rep. Med. Chem.* **1996**, *31*, 91 - 100. b) Ojima, I.; Chakravarty, S.; Dong, Q., *Bioorg. & Med. Chem.*, **1995**, *3*, 337-360. c) 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. d) Cook, N. S.; Kottirsch, G.; Zerwes, H.-G. *Drugs of the Future* **1994**, *19*, 135 - 159. e) Nichols, A. J.; Ruffolo, R. R., Jr.; Huffman, W. F.; Poste, G.; Samanen, J. *Trends in Pharmaceutical Sciences* **1992**, *13*, 413 - 417.
8. 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.
9. Ali, F. E.;. Bennett, D. B.; Calvo, R. R.; Elliott, J. D.; Hwang, S. M.;. Ku, T. W.; Lago, M. A.; Nichols, A. J.; Romoff, T. T.; Shah, D. H.; Vasko, J. A.; Wong, A. S.; Yellin, T. O.; Yuan, C. -K.; Samanen, J. M. *J. Med. Chem.* **1994**, *37*, 769-780.
10. 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.
11. 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, Mayflower Scientific, **1996**, 670-681.
12. Miller, W. H., Ku, T. W., Ali, F. E., Bondinell, W. E., Calvo, R. R., Davis, L. D., Erhard, K. F., Hall, L. B. Huffman, W. F., Keenan, R. M., Kwon, C. Newlander, K. A., Ross, S. T., Samanen, J. M., Takata, D. T., and Yuan, C. -K. *Tetrahedron. Lett.* **1995**, *36*, 9433-9436.
13. Muller, W. and Stauss, U., *Helv. Chim. Acta.* **1982**, *65*, 2118-2132. b) 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**).
14. All new compounds gave satisfactory spectroscopic and analytical data.
15. Chiral HPLC conditions: For compound **10b**: CHIRALPAK AD; 4.6 x 250 mm; 90:10:0.1 = Hexane:Ethanol:Triethylamine; 1.0 mL/min; UV detection at 254 nM; t_R (*R*) = 18.6 min; t_R (*S*) = 20.9 min. For compound **5**: 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 compound **14**: CHIRALCEL OD-R; CH_3OH ; 4.6 x 250 mm; 0.6 mL/min; UV detection at 254 nM; t_R (*R*) = 16.3 min; t_R (*S*) = 19.1 min.
16. Although the three-step transformation is a relatively simple process, **12** must be desalted through a XAD-2 column. The resulting lyophilized powder is difficult to dry, which may contribute to a lower-than-expected yield in the final cyclization step.

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