Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 1989–1992

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A Short Synthesis of Argatroban: A Potent Selective Thrombin Inhibitor

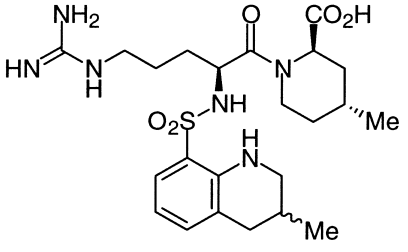
Janine Cossy* and Damien Belotti

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

Received 9 March 2001; revised 14 May 2001; accepted 16 May 2001

Abstract—Argatroban was synthesized in seven steps from 4-methylpiperidine. The condensation of (±)-*trans*-benzyl 4-methylpipecolic acid ester with N^{α}-Boc-N^{ω}-nitro-L-arginine led to two diastereomers that were separated. One of them is the precursor of argatroban.

Thrombotic vascular disease is a major cause of mortality in the industrialized world. Thrombin, a trypsin-like serine protease and a key enzyme in the blood coagulation cascade, plays a major role in the development of the disease state, catalyzing the formation of polymerizable fibrin from fibrinogen as well as stimulating platelet aggregation. The currently used antithrombotics, heparin and coumarins, suffer from well-documented liabilities. Antithrombotics with an immediate onset of action are attractive targets. Considerable effort has recently been directed towards the development of inhibitors of thrombin. Hirudin,[1] a polypeptide isolated from the medicinal leech, is in phase III clinical trials[2] as is hirulog,[3] one of a series of peptide inhibitors derived from hirudin. A variety of low molecular weight thrombin inhibitors are also under investigation.[4] Independent lines of development led to the identification of the lead inhibitor argatroban.



Argatroban **1**

Argatroban **1**, (2*R*,4*R*)-4-methyl-1-[N^2-(3-methyl-1,2,3,4-tetrahydro-8-quinolinesulfonyl)-L-arginyl]-2-piperidinecarboxylic acid, is a known potent competitive inhibitor of the enzyme thrombin, with a 50% inhibition (IC_{50}) of 9 nM against thrombin-induced platelet aggregation and has clinical potential in maintenance anticoagulation therapy.[5–10] This compound is a potent, selective efficacious reversible-binding thrombin inhibitor[11] with a short duration of action that has been approved as a parenteral antithrombotic in Japan.[12] The synthesis of argatroban was achieved from 4-methyl-2-piperidine carboxylic acid. Although the 4-methyl-2-piperidine carboxylic acid moiety is introduced as a stereochemically and enantioselectively defined synthon, the final step of the synthesis of argatroban creates an additional stereochemical center during the reduction of the 3-methylquinoline sulfonamide **8′** and concomitant deprotection of the nitroguanidine. This results in the generation of argatroban as a roughly 64/36 mixture of 21-(*R*)- and 21-(*S*)-diastereomers **1a** and **1b** (Scheme 1). This synthesis of argatroban requires the synthesis of the optically pure **7′** from the ethyl (2*R*,4*R*)-4-methylpipecolic acid ester **5′**. This latter compound was obtained either from 2,4-dimethylpyridine or 4-methylpyridine in, respectively, six and seven steps after resolution by crystallization with L-tartaric acid.[13] Argatroban was synthesized in 11 and 12 steps, respectively, from 2,4-dimethylpyridine or 4-methylpyridine.

For our part, we envisaged the synthesis of argatroban from a mixture of diastereomeric benzyl esters **7**. Compounds (L,*R*,*R*)-**7a** and (L,*S*,*S*)-**7b** should be the result of the coupling reaction between (±)-*trans*-benzyl 4-

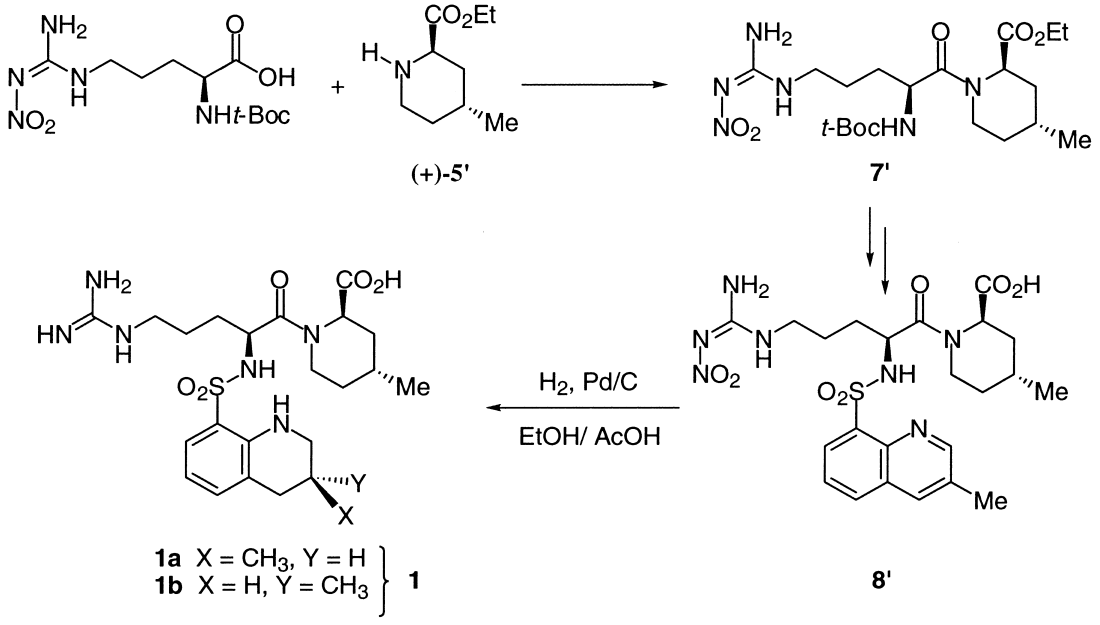
*Corresponding author. Tel.: +33-1-4079-4429; fax: +33-1-4079-4660; e-mail: janine.cosy@espci.fr

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00351-1

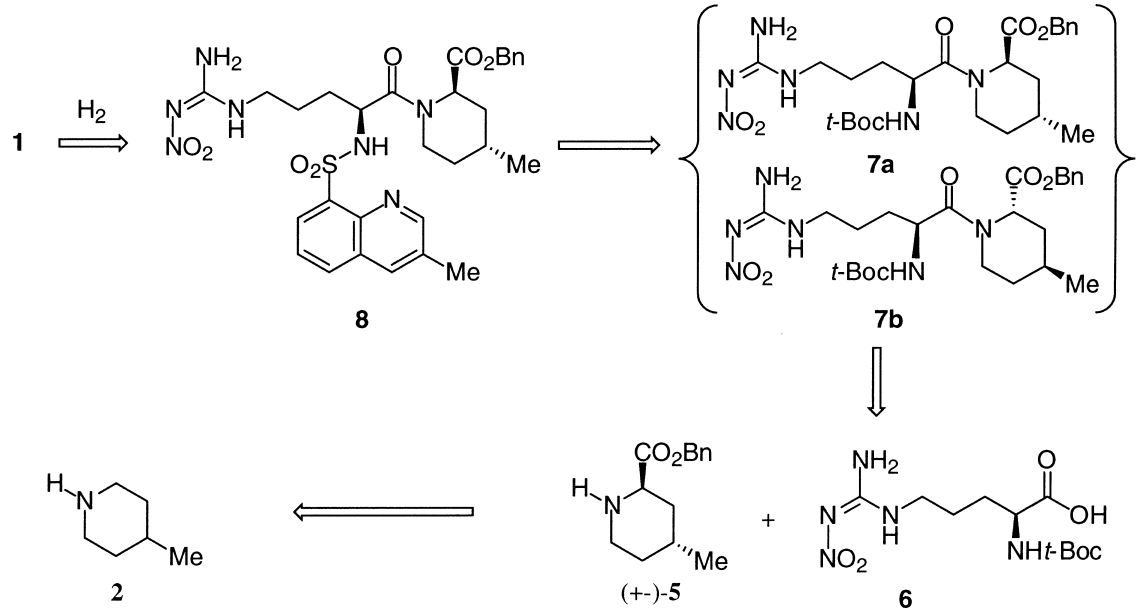
methylpipecolic acid ester **5** and N^{α}-Boc-N^{ω}-nitro-L-arginine **6** and should be separable. After the transformation of **7a** into compound **8**, *N*-Boc deprotection and a one-pot three-step hydrogenation should lead to argatroban. This hydrogenation should cleave the benzyl ester group, the nitro group of the arginine, and reduce the pyridine ring (Scheme 2).

The synthesis of (±)-*trans*-benzyl 4-methyl pipecolic acid ester was achieved in three steps. The 4-methylpiperidine **2** was transformed to the *N*-Boc piperidine **3** (Boc_2O, Et_3N, CH_2Cl_2, 0 °C to rt) in quantitative yield, which after a lithiation–alkoxycarbonylation sequence using benzyl chloroformate (*s*-BuLi, TMEDA, Et_2O, −90 °C; $ClCO_2Bn$, −90 °C to rt; yield = 35%) afforded the benzyl *trans*-*N*-Boc-4-methylpipecolic acid ester (±)-**4** with a *trans*/*cis* diastereoselectivity up to 95/5.[14] After *N*-Boc deprotection (HCl, AcOEt, 0 °C to rt, yield: 99%), the desired benzyl 4-methyl pipecolic acid ester (±)-**5** was obtained with an overall yield of 34% from 4-methylpiperidine (Scheme 3).

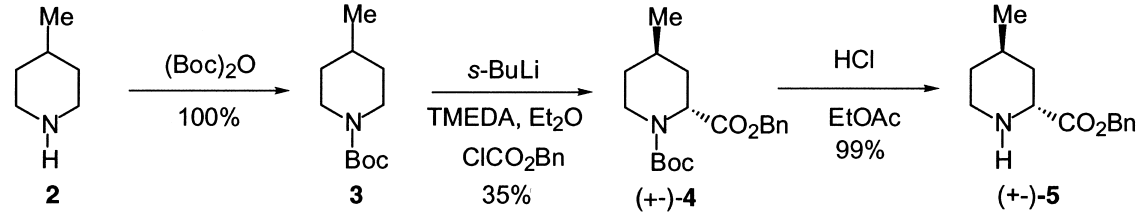
The condensation of compound (±)-**5** with N^{α}-(*tert*-butoxycarbonyl)-N^{ω}-nitro-L-arginine **6**, by the mixed anhydride method,[15] using isobutyl chloroformate (1 equiv) and Et_3N (1 equiv) at −35 °C, led to a mixture of two diastereomers **7a**/**7b** in a ratio of 1 to 1 in 58% yield. These two diastereomers were separated by flash chromatography on silica gel (eluent, CH_2Cl_2/EtOH: 97/3) to afford the desired (L,*R*,*R*)-**7a** in 29% yield.[16]



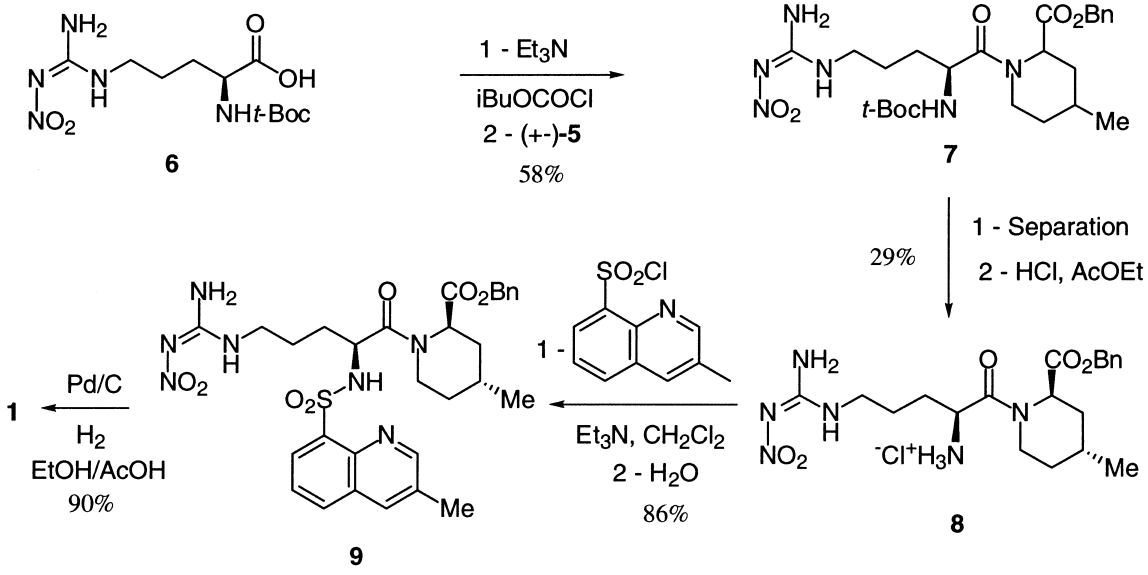
Scheme 1. Synthesis of argatroban **1** by Mitsubishi.



Scheme 2. Retrosynthetic scheme.



Scheme 3. Synthesis of the pipecolic acid derivative.



Scheme 4. Synthesis of argatroban.

After removal of the *tert*-butoxycarbonyl group by HCl/AcOEt at rt, in quantitative yield, compound **8** was transformed to **9** by treatment with 3-methyl-8-quinoline sulfonyl chloride (Et_3N, CH_2Cl_2, 0 °C; yield: 86%). As expected, the hydrogenation of **9** on Pd/C (10% Pd/C; H_2; 1 atm; EtOH, AcOH; rt) effected the debenzylation of the ester group, the cleavage of the nitro group and the hydrogenation of the pyridine ring affording argatroban monohydrate in 90% yield after recrystallization from EtOH/H_2O, in a 65:35 ratio of the 21-(*R*)/21-(*S*) diastereomers[13] (mp: 177–181 °C, $[\alpha]_D^{25}$ +78 (*c* 1, 0.2 N HCl)[12a,17] (Scheme 4).

The synthesis of argatroban was achieved in seven steps from (±)-4-methylpiperidine. This synthesis is shorter and more efficient than the synthesis described previously due to the separation of the diastereomers **7a** and **7b** and the use of the (±)-*trans*-benzyl 4-methylpipecolic acid ester instead of the *trans*-ethyl 4-methylpipecolic acid ester.

References and Notes

1. Markwardt, F. *Thromb. Haemost.* **1991**, *66*, 141.
2. (a) Vandenbos, A. A.; Deckers, J. W.; Heyndrickx, G. R.; Laarman, G. J.; Suryapranata, H.; Zijlstra, F.; Close, P.; Rijnierse, J. J. M. M.; Buller, H. R.; Serruys, P. W. *Circulation* **1993**, *88*, 2058. (b) Kruse, H.-J.; Mayerhofer, C.; Siess, W.; Weber, P. C. *Am. J. Physiol.* **1995**, *268*, C36. (c) Albrightson, C. R.; Pullen, M.; Wu, H.-L.; Dytko, G.; Hersh, L. B.; Nambi, P. *Mol. Pharmacol.* **1995**, *47*, 1156.
3. (a) Topol, E. J.; Bonan, R.; Jewitt, D.; Sigwart, U.; Kakkar, V. V.; Rothman, M.; de Bono, D.; Fegurson, J.; Willerson, J. T.; Strony, J.; Ganz, P.; Cohen, M. D.; Raymond, R.; Fox, I.; Maranganore, J.; Adelman, B. *Circulation* **1993**, *87*, 1622. (b) Cicala, C.; Bucci, M.; De Dominicis, G.; Harriot, P.; Sorrentino, L.; Cirino, G. *Br. J. Pharmacol.* **1999**, *126*, 478.
4. (a) Taparelli, C.; Metternich, R.; Ehrhardt, C.; Cook, N. S. *Trends Pharmacol. Sci.* **1993**, *14*, 366. (b) Nöteberg, D.; Branalt, J.; Kvarnström, I.; Linschoten, M.; Musil, D.; Nyström, J.-E.; Zuccarello, G.; Samuelsson, B. *J. Med. Chem.* **2000**, *43*, 1705 and references cited therein.
5. Bush, L. R. *Cadiosvasc. Drug Rev.* **1991**, *9*, 247.
6. Okamoto, S.; Hijikata, A.; Kikumoto, R.; Tamao, Y.; Ohkubo, K.; Tezuka, T.; Tonamura, S.; US Patent, 4,101,653, 1978.
7. Brundish, D.; Bull, A.; Donovan, V.; Fullerton, D. J.; Garman, S. M.; Hayler, J. F.; Janus, D.; Kane, P. D.; McDonnell, M.; Smith, G. P.; Wakeford, R.; Walker, C. V.; Howarth, G.; Hoyle, W.; Allen, M. C.; Ambler, J.; Butler, K.; Talbot, M. D. *J. Med. Chem.* **1999**, *42*, 4584.
8. Kikumoto, R.; Tamao, Y.; Tezuka, T.; Tonamura, S.; Hara, H.; Ninomiya, K.; Hijikata, A.; Okamoto, S. *Biochemistry* **1984**, *23*, 85.
9. Shebuski, R. J. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic: San Diego, 1999; Vol. 26, p 98.
10. Strupczewski, J. D.; Ellis, D. B.; Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic: San Diego, 1991; Vol. 26, p 299.
11. (a) Reviews: Taparelli, C.; Metternich, R.; Ehrhardt, C.; Cook, N. S. *Trends Pharmacol. Sci.* **1993**, *14*, 366. (b) Jakubowski, J. A.; Smith, G. F.; Sall, D. J. *Annu. Rep. Med. Chem.* **1992**, *27*, 99.

12. (a) Okamoto, S.; Hijikata, A.; Kikumoto, R.; Tonamura, S.; Hara, H.; Ninomiya, K.; Maruyama, A.; Sugano, M.; Tamao, Y. *Biochem. Biophys. Res. Commun.* **1981**, *101*, 440. (b) Hijikata-Okunomiya, A.; Okamoto, S. *Semin. Thromb. Hemostasis* **1992**, *18*, 135.
13. (a) US Patent 4,201,863, 1980; Appl. 622,390, 14 Oct 1975 (Mitsubishi); Jpn. Kokai Tokkyo Koho 81/15, 267, 1981; Appl. 79/88, 786, 13 Jul 1979 (Mitsubishi). (b) US Patent 4,258,192, 1981; Appl. 622,390, 14 Oct 1975; Jpn. Kokai Tokkyo Koho 81/15, 267, 1981; Appl. 79/88, 786, 13 Jul 1979 (Mitsubishi). (c) Eur. Pat. Appl. 8746, 1980; US Appl 938, 711, 31 Aug 1978 (Mitsubishi).
14. Cossy, J.; Belotti, D. *Tetrahedron Lett.* **2001**, *42*, 2119.
15. Kikumoto, R.; Tamao, Y.; Ohkubo, K.; Tezuka, T.; Tonomura, S.; Okamoto, S.; Funahara, Y.; Hijikata, A. *J. Med. Chem.* **1980**, *23*, 830.
16. Compound **7a** is the more polar diastereomer on silica gel (CH_2Cl_2/EtOH 97:3).
17. Lit., mp: 176–180 °C; $[\alpha]_D^{27}$ +76 (*c* 1, 0.2 N HCl).[12a]