Tetrahedron Letters Vol 32, No 42 pp 6019-6020, 1991
Printed in Great Britain

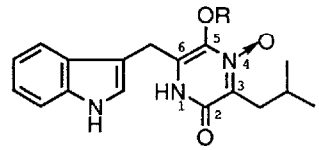
0040-4039/91 $3 00 + 00
Pergamon Press plc

TOTAL SYNTHESIS OF A NEW INHIBITOR OF SUPEROXIDE ANION GENERATION, OPC-15161

Yasuyuki KITA,* Shuji AKAI, Hiromichi FUJIOKA, and Yasumitsu TAMURA,
Faculty of Pharmaceutical Sciences, Osaka University,
1-6, Yamada-oka, Suita, Osaka 565, JAPAN
Hitoshi TONE and Youichi TANIGUCHI
Research Institute, Otsuka Pharmaceutical Co , Ltd ,
463-10, Kagasuno, Kawauchi-cho, Tokushima 771-01, JAPAN

Summary The first total synthesis of a new inhibitor of superoxide anion generation, OPC-15161, was achieved from tryptophan methyl ester in 4-6 steps in 9 9-10 6% overall yields

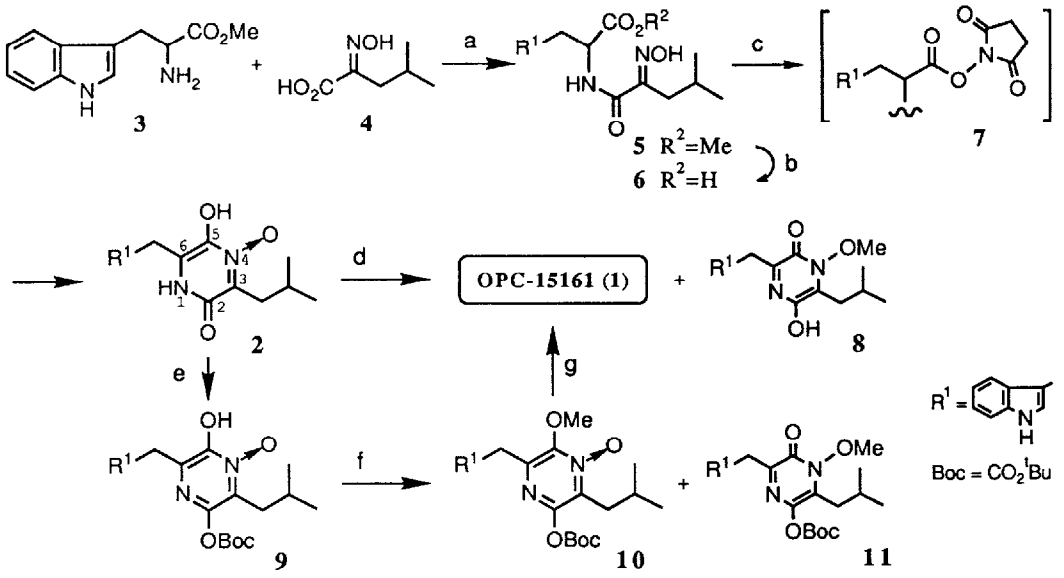
Very recently a new inhibitor of superoxide anion generation, OPC-15160, was isolated from the culture broth of fungus *Thielavia minor* OFR-1561, and a more active inhibitor, OPC-15161, was obtained as a major degradation product of OPC-15160 [1] OPC-15161 showed potent inhibitory activity (IC_{50} 2 8x10^{-5} M) on superoxide anion generation by guinea pig peritoneal macrophages Recent studies on the causal relation of superoxide anion released by macrophages or neutrophiles and production tissue damage in ischemic or inflammatory processes imply a promising chemotherapeutic potential of OPC-15161 for ischemic or inflammatory diseases [2] Elucidation of the exact structure of OPC-15161 by X-ray analysis revealed a novel and highly oxygen-functionalized pyrazine ring having an indole-side chain (**1**) Because of its strong therapeutic potency and a unique structure, we are very much interested in the total synthesis of **1** Here we wish to describe the first total synthesis of **1** *via* the 2,5-dioxygenated pyrazine 4-oxide precursor (**2**) obtained from tryptophan methyl ester (**3**)



OPC-15161 (**1**) R=Me
2 R=H

Condensation of tryptophan methyl ester (**3**) and α-hydroxyimino carboxylic acid (**4**) with DCC and *N*-hydroxysuccinimide (HOSu) in dioxane gave the amide (**5**) in 95% yield Though direct cyclization of **5** must be the best method for **2**, the reaction did not occur even under rigorous conditions such as excess *p*-TsOH or DBU in refluxing dioxane Next, activation of the carboxylic acid (**6**), obtained quantitatively by alkaline hydrolysis of **5** and the subsequent cyclization were studied After many unsuccessful results by using usual dehydrative condensation methods for macrolide synthesis,[3] treatment of **6** by Mukaiyama's method[4] [Ph_3P (2 equiv) and 2,2'-dipyridyl disulfide (2 equiv)] in THF under careful reaction conditions (at room temperature for 1 h) gave the desired **2** in up to 12% yield Increasing the amount of the reagents, addition of DMAP or AcOH, higher temperature, and longer reaction time resulted in giving complex mixtures owing to decomposition of **2** The use of a powerful condensation reagent, (trimethylsilyl)ethoxyacetylene[5] in CH_3CN at 45 °C for 6 h provided **2** in 15-20% yield accompanied with about 20% yield of recovered **6** Finally, treatment of **6** with DCC and HOSu in dioxane at room temperature yielded the *N*-carboxyimide (**7**), which was cyclized with AcONa to give a 52% yield of **2**

Another subject was site-selective methylation at the C-5 hydroxyl group of **2**, since **2** has four reactive centers, N-1, C-2 carbonyl, N-4 oxide, and C-5 hydroxyl groups, on a pyrazine ring Preliminary methylation by excess MeI-K_2CO_3 or CH_2N_2 gave a mixture of dimethylated products at 1,5-, 2,4-, and 2,5-positions with-



a DCC (1 equiv), HOSu (1 1 equiv), dioxane, r t 1 d, b 1N NaOH, EtOH, r t , 30 min, c i) DCC (1 2 equiv), HOSu (1 1 equiv), dioxane, r t , 1 h, ii) AcONa (1 0 equiv), r t , 2 h, d i) DBU (1 equiv), DMF, 0 °C, ii) $Me_3O^+BF_4^-$ (2 equiv), CH_2Cl_2, -10 °C, 30 min, e $(Boc)_2O$ (1 1 equiv), Et_3N (1 equiv), DMAP (0 1 equiv), DMF, -5 °C, 30 min, f CH_2N_2 (excess), BF_3OEt_2 (cat), CH_2Cl_2-MeOH (3 1), r t , overnight, g CF_3CO_2H, CH_2Cl_2, r t , 1 h

out formation of **1** Although various methylation methods (employing methyl sulfonate derivatives and methyloxonium or methylsulfonium salts) were tried, only $Me_3O^+BF_4^-$-treatment of DBU salt of **2** could provide the desired **1** in 20% yield accompanied with the regioisomer (**8**) in 40% yield An alternative three-step approach from **2** also gave **1** in nearly the same yield (22%) After selective protection of the C-2 carbonyl group by treatment with $(Boc)_2O$, Et_3N, and DMAP in 63% yield, the Boc derivative (**9**) was methylated with CH_2N_2 in the presence of a catalytic amount of BF_3OEt_2 to give a mixture (1 1 6) of **10** and **11** quantitatively Deprotection of **10**, separated by preparative TLC on silica gel, with CF_3CO_2H gave **1** in 34% yield from **9** Thus obtained **1** was in all respect identical with the natural OPC-15161 [6]

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2 J A Badway and M L Larnovsky, *Annu Rev Biochem* , **49**, 695 (1980), B A Freeman and J D Crapo, *Lab Invest* , **47**, 412 (1982), P A Ward R E Duque, M C Sulavik, and K J Johnson, *Am J Pathol* , **110**, 297 (1983), S J Weiss, *Acta Physiol Scand (Suppl)*, **548**, 9 (1986), K Taniguchi, M Urakami, and K Takanaka, *Jpn J Pharmacol* , **46**, 275 (1988)

3 For instance, treatment of **6** with 2,4,6-trichlorobenzoyl chloride-Et_3N-DMAP, N,N'-cabonyldiimidazole, $(CF_3CO)_2O$, or cyanuric chloride-Et_3N gave complex mixtures

4 T Mukaiyama, R Matsueda, and M Suzuki, *Tetrahedron Lett* , **1970**, 1901

5 Y Kita, S Akai, N Ajimura, M Yoshigi, T Tsugoshi, H Yasuda, and Y Tamura, *J Org Chem* , **51**, 4150 (1986), Y Kita, S Akai, M Yamamoto, M Taniguchi, and Y Tamura, *Synthesis*, **1989**, 334

6 All new compounds were characterized by ^1H NMR, IR, and MS data and gave satisfactory analytical and/or high resolution MS data Their melting points are as follows **5**, 123-124 °C (Et_2O-hexane), **6**, 97-98 °C (CH_2Cl_2), **2**, 166-168 °C (decomp), **1**, 225-227 °C (lit [1] 223 5-225 5 °C), **9**, 230-240 °C ($^iPr_2O$) (decomp), **10**, gum

(Received in Japan 24 July 1991)