Pergamon

Tetrahedron Letters, Vol. 35, No. 13, pp. 2061-2062, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0174-V

Rapid, Practical Syntheses of the Arginyl Polyamine sFTX-3.3: a Blocker of Voltage-Sensitive Calcium Channels

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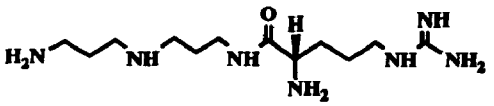
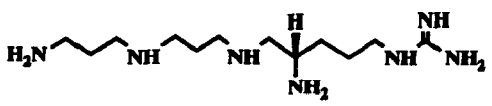
Abstract: sFTX-3.3, a polyamine toxin analogue, has been synthesized from tri-CBZ-L-arginine. Rapid, practical procedures to prepare this calcium channel blocker are presented.

Arthropod polyamine toxins and their synthetic analogues are useful pharmacological tools for the identification of different types of voltage-sensitive calcium channels [1, 2]. These toxins display a variety of effects on different subclasses of calcium channels and selective channel blockers are required in order to delineate the physiological functions of these ion channels. Recently, a synthetic polyamine amide sFTX-3.3 (also called sFTX, arginine polyamine) (1) and a putative polyamine from American funnel-web *Agelenopsis aperta* venom FTX-3.3 (FTX) (2) have been shown to inhibit voltage-activated calcium channels. The selectivity of these polyamine amides remains in question. Although (2) inhibits P-type calcium channels [3, 4, 5, 6], (1) reversibly inhibits low voltage-activated T-type calcium currents in cultured neurones at 10 nM [7, 8]. Quantities of these spider toxins and synthetic polyamine amides [9] are required for biological assessment and therefore we have completed the synthesis of (2) [10] as well as seeking a facile route to (1). In this *Letter*, we report rapid, practical procedures for the synthesis of (1). The amino acid residue L-arginine contains the guanidine of (1) and therefore any practical synthesis will require the addition of a (suitably protected) triamine to an activated and protected arginine generating a new amide bond.

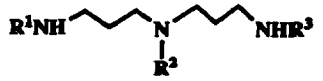


(1) sFTX-3.3 (sFTX)



(2) FTX-3.3 (FTX)

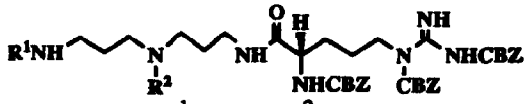
Initially, we decided to synthesize (1) by a peptide coupling reaction between mono-BOC-3,3'-iminobispropylamine (3) and tri-CBZ-L-arginine (4). Symmetrical triamine (5) was mono-BOC protected on a primary amino functional group by treatment of (5) (3 equiv.) dropwise (3 h) with di-*tert*-butyldicarbonate, in anhydrous THF, 0°C to 25°C over 18 h followed by chromatography (SiO_2; CH_2Cl_2/MeOH/conc. NH_4OH, 100:10:1 to 10:4:1) (81%). These are efficient modifications to the reported procedures [11, 12] which use significantly less polyamine and afford a high yield of (3). Protected polyamine (3) was coupled to (4) (DCC, HOBt, 16 h), in CH_2Cl_2, and, after silica gel chromatography, the desired amide (6) was obtained as a white solid (30%). Sequential deprotection of the amines, TFA (0°C, 30 mins) followed by hydrogenolysis (10% Pd/C, 1 atm, 16 h), gave sFTX-3.3 (1) as a white solid (70%), 17% over four steps from triamine (5).



(3) $R^1 = BOC; R^2 = R^3 = H$
(5) $R^1 = R^2 = R^3 = H$
(9) $R^1 = R^2 = CBZ; R^3 = H$

CBZ = $PhCH_2OCO$

BOC = Me_3COCO



(6) $R^1 = BOC; R^2 = H$
(8) $R^1 = R^2 = H$
(10) $R^1 = R^2 = CBZ$

(4) R = H
(7) R = *N*-succinimide

In the simplest and most rapid synthesis of sFTX-3.3 (1), triamine (5) (3 equiv.) was coupled to available (Novabiochem) *N*-hydroxysuccinimide activated ester (7), in CH_2Cl_2 (25°C, 16 h), to afford amide (8) after silica gel chromatography (48%). Quantitative removal of the three CBZ-protecting groups in (8), by hydrogenolysis (10% Pd/C, 1 atm, 16 h), afforded (1) as the free base. Thus, (1) has been prepared in only two steps and in 48% overall yield from triamine (5). The highest yielding route to (1) was the coupling of *N*, *N'*-diCBZ-bisiminopropylamine (9) [10] with tri-CBZ-L-arginine (4) which afforded the protected amide (10) (83%). Hydrogenolysis (10% Pd/C, 1 atm, 16 h) of (10) yielded (1) quantitatively. The efficient preparation of (9) [10] means that, from triamine (5), the calcium channel blocker sFTX-3.3 (1) has been prepared in 58% overall yield.

Acknowledgements: We acknowledge the financial support of AFRC (86/521) and The Nuffield Foundation (SCI/180/91/15/G). Pharmacological testing was also supported by MRC (G9219134N and G9219146N) and The Wellcome Trust (039750). We are grateful to Dr R H Scott, St. George's Hospital Medical School, University of London, for useful discussions throughout this project.

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(*Received in UK* 16 *December* 1993; *revised* 19 *January* 1994; *accepted* 20 *January* 1994)