Pergamon

Tetrahedron Letters 42 (2001) 6999–7001

TETRAHEDRON LETTERS

Total synthesis of (±)-homopumiliotoxin 223G

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Received 20 February 2001; revised 17 April 2001; accepted 27 July 2001

Abstract—The total synthesis of (±)-homopumiliotoxin 223G was achieved in six steps and 14% yield through the addition of 5-methyl-2-triisopropylsilyoxyfuran (**3**) to the *N*-acyliminium ion derived from *N*-Cbz 2-methoxypiperidine featuring bicyclic lactam **9b** as the key intermediate.

Amphibian skin has provided a wide range of biologically active alkaloids, many of which have unique profiles of pharmacological activity and therapeutic potential. Among them pumiliotoxins, allo- and homopumiliotoxins were shown to have myotonic and cardiotonic activity.[1] It appears likely that these alkaloids are taken up into the skin from the diet, which for such amphibians consists mainly of small arthropods.[2] The compounds are stored in granular skin glands and are released as defense against predators.[3] In this communication, we report a short approach to the synthesis of homopumiliotoxin alkaloids (Fig. 1). Recently, the total synthesis of (–)-homopumiliotoxin 223G was achieved by Kibayashi et al.[4]

The synthetic route envisioned for homopumiliotoxin 223G features the preparation of bicyclic lactam **9**, the key intermediate in our approach, through the addition of silyloxyfuran **3** to *N*-acyliminium ion **2**.

As described in our previous communication,[5] the vinylogous Mannich addition[6] of silyloxyfuran **3**[7,8] to the *N*-acyliminium derived from **2a**,**b** provided *erythro*-**4a**,**b** as the major diastereoisomer when the reaction was carried out in CH_2Cl_2 and catalytic TMSOTf was used to generate the corresponding *N*-acyliminium ion. Different solvents and Lewis acids were sought in order to improve the yield of *threo*-**5a**, which displays the relative configuration required for (±)-**1** (Scheme 1 and Table 1).

As previously noticed by Morimoto in the study of the addition of silyloxyfurans to the five-membered *N*-acyliminium ring,[9] diastereoselectivity was not significantly affected neither by the nature of the Lewis acid nor by the solvent (*erythro*-**4a**:*threo*-**5a** = 1.1:1–2:1), except when a binary solvent system (1:1 CH_2Cl_2:THF, v/v) was used. In fact, in the presence of TMSOTf the preference for the *erythro* isomer **4a** increased (Table 1, entry 10). The use of **2b** (R_1 = Boc) did not improve the yield of *threo*-**5b** but provided significant amounts of regioisomer **6b** (stereochemistry not determined), particularly when $BF_3{\cdot}OEt_2$ was used as the Lewis acid.[4]

The relative configurations of **4a** and **5a** were established after their conversion into the corresponding bicyclic lactam **9a** and **9b**,[10] followed by NOE experi-

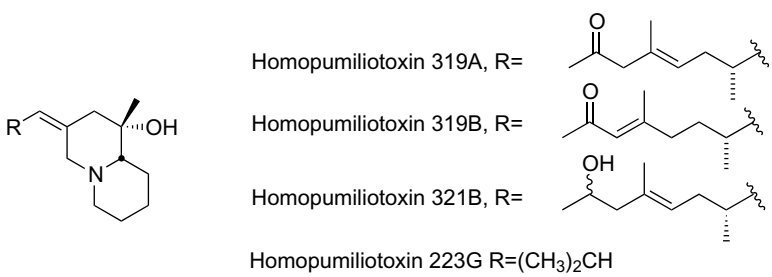

Figure 1. Representative homopumiliotoxin alkaloids.

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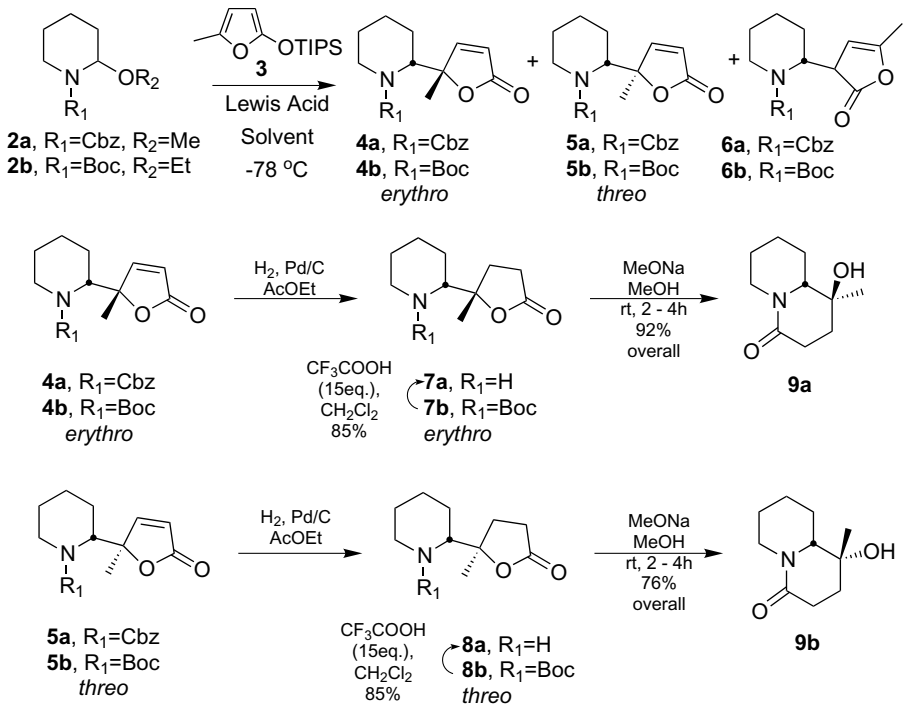


Scheme 1. Vinylogous Mannich reaction of **3** and **2a**/**2b** and conversion to lactams **9a** and **9b**.

Table 1. Addition of silyloxyfuran **3** to carbamates **2a** and **2b**

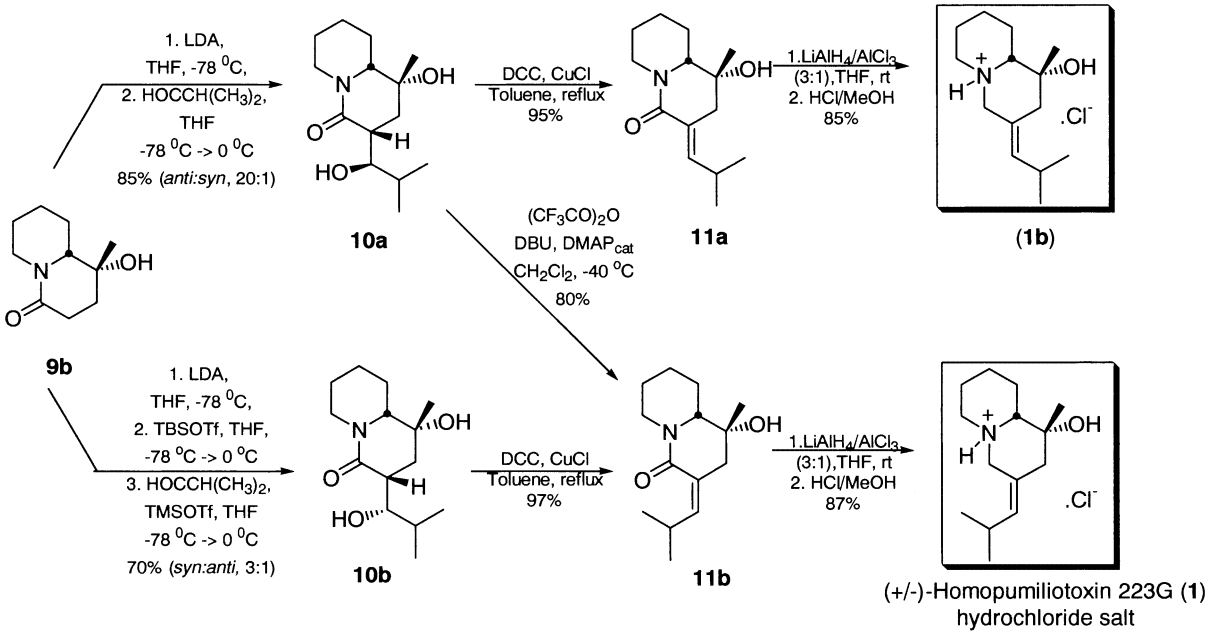
Entry	R	Solvent	Lewis acid	**4**:**5**:**6**[a]	Yield (%)[b]
1	Cbz	CH_2Cl_2	TMSOTf	2:1:0	85
2	Cbz	CH_2Cl_2	$TiCl_4$	1.2:1:0	70
3	Cbz	CH_2Cl_2	$BF_3{\cdot}OEt_2$	1.2:1:0	50
4	Cbz	Et_2O	TMSOTf	1.1:1:0	65
5	Cbz	Et_2O	$TiCl_4$	1.2:1:0	58
6	Cbz	Et_2O	$BF_3{\cdot}OEt_2$	1.1:1:0	50
7	Cbz	THF	TMSOTf	1.3:1:0	55
8	Cbz	THF	$TiCl_4$	–	–
9	Cbz	THF	$BF_3{\cdot}OEt_2$	1.1:1:0	42
10	Cbz	THF/CH_2Cl_2	TMSOTf	6:1:0	80
11	Cbz	THF/CH_2Cl_2	$TiCl_4$	–	–
12	Cbz	THF/CH_2Cl_2	$BF_3{\cdot}OEt_2$	1.4:1:0	43
13	Boc	THF/CH_2Cl_2	TMSOTf	18.5:1:11	67
14	Boc	THF/CH_2Cl_2	$TiCl_4$	–	–
15	Boc	THF/CH_2Cl_2	$BF_3{\cdot}OEt_2$	15:1:9.8	40

[a] Diastereoselectivity determined by GC and confirmed by ^1H NMR analyses.
[b] Yields determined after column chromatography on silica gel of the crude product.

ments as described in our previous communication and next we focused on the installation of the isobutylidene moiety present in (±)-**1**.

We first explored the reaction of the preformed lithium enolate of **9b** (LDA, 2 equiv., −78°C) with isobutyraldehyde, which afforded a 20:1 mixture of two aldol adducts **10a**:**10b** in 85% yield. The *anti* configuration of the major isomer **10a** was determined after stereospecific *syn* elimination using DCC/CuCl,[11] which gave **11a** in 95% yield. Accordingly, *anti* elimination of **10a** using Stork protocol[12] afforded **11b** in 80% yield. The assignment of the double bond configuration in **11a** and **11b** was rather straightforward upon inspection of their ^1H NMR spectra due to the characteristic deshielding of the olefinic hydrogen in **11a** (δ 6.81) when compared with the same signal in **11b** (δ 5.60) due to the anisotropy of the carbonyl group (Scheme 2).[13]

Alternatively, Mukaiyama aldol reaction of the *N*,*O*-silylketeneacetal derived from **9b**[14] and isobutyraldehyde catalyzed by TMSOTf afforded a 3:1 mixture of **10b**:**10a**. Stereospecific *syn* elimination using DCC/CuCl[11] gave **11b** in 97% yield. Once an efficient approach to bicyclic lactam **11b** was secured, the completion of the total synthesis of (±)-homopumiliotoxin 223G (**1**)[15] required AlH_3 reduction,[16] which was accomplished in 87% yield (Scheme 2). Its identity was



Scheme 2. Total synthesis of (±)-homopumiliotoxin 223G.

established after comparison of its ^{1}H and ^{13}C NMR data with those reported by Kibayashi et al.[4b]

Acknowledgements

We thank Fapesp and CNPq for financial support and fellowships.

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10. Analytical data. Compound **5a**: ^{1}H NMR ($CDCl_3$, 500 MHz, 293 K): δ 1.41 (s, 3H), 1.30–1.50 (m, br, 1H), 1.50–1.70 (m, br, 3H), 1.75–1.85 (m, br, 1H), 1.90–2.05 (m, br, 1H), {[2.65–2.75 (m, br) and 2.82 (t, $J=12.6$ Hz)], 1H}, {[3.91 (d, $J=12.6$ Hz) and 4.0–4.1 (m, br)], 1H}, 4.30 (s, br, 1H), 4.98 (d, $J=12.0$ Hz, 1H), 5.03 (d, $J=12.0$ Hz, 1H), 5.74 (d, $J=5.5$ Hz, 1H), 7.2–7.5 (m, 6H); ^{13}C NMR ($CDCl_3$, 125.7 MHz, 293 K): δ 19.4, 22.2, 23.6, 24.3, 41.1, 54.9, 67.5, 93.4, 119.4, 127.9, 128.3, 128.7, 136.8, 156.3, 160.8, 173.1. Compound **9b**: ^{1}H NMR ($CDCl_3$, 500 MHz, 293 K): δ 1.34 (s, 3H), 1.40–1.50 (m, 3H), 1.52–1.70 (m, 2H), 1.76 (ddd, $J=5.6$, 10.7 and 16.6 Hz, 1H), 1.82–1.88 (m, 3H), 2.30–2.45 (m, 2H), 2.62 (ddd, $J=5.6$, 10.7 and 16.1 Hz, 1H), 3.07 (d, br, $J=11.3$ Hz, 1H), 4.79 (d, br, $J=13.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 24.3, 25.0, 26.2, 27.4, 28.5, 33.3, 43.2, 65.5, 67.9, 169.1; HRMS (70 eV): 183.1255; calcd for $C_{10}H_{17}NO_2$: 183.1259.
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