Pergamon

Tetrahedron 56 (2000) 7969–7973

TETRAHEDRON

New Synthesis of the Alkaloid Polonicumtoxin C

Tuyen Nguyen Van and Norbert De Kimpe*

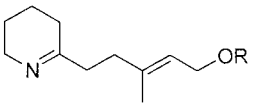
Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

Received 12 May 2000; revised 17 July 2000; accepted 3 August 2000

Abstract—Two new short syntheses of the alkaloid polonicumtoxin C (**3**) are presented. In the first pathway, polonicumtoxin C was obtained in two steps by alkylation of 6-methyl-2,3,4,5-tetrahydropyridine with *E*-4-bromo-3-methyl-1-(tetrahydro-2-pyranyloxy)-2-butene **7** and subsequent deprotection of the THP group. In the second pathway, the cyclic ketimine was constructed via a short sequence of reactions involving (a) sequential alkylation of the *N*-(isopropylidene)isopropylamine with *N*,*N*-disilylprotected ω-bromopropylamine and *E*-4-bromo-3-methyl-1-(tetrahydro-2-pyranyloxy)-2-butene **7**, (b) transimination and deprotection, the latter two reactions occurring in one step.

Introduction

The blooms of the fresh water dinoflagellate *Peridinium* spp. cause serious environmental problems in man-made lakes in Japan, because most of the affected lakes are used as reservoirs for water supply.[1] These blooms were also found to be responsible for fish killed in these lakes. The toxic principles of *Peridinium polonicum* have been isolated and characterized as polonicumtoxin A (**1**), polonicumtoxin B (**2**) and polonicumtoxin C (**3**).[2] These tetrahydropyridine alkaloids exhibit an extremely potent toxicity towards fish, comparable to the ichtyotoxicity of the marine dinoflagellate brevetoxin B.[2] Recently, synthetic routes for these polonicumtoxins were reported, securing the determination of the olefin geometry of these alkaloids as *E*.[2] One synthetic strategy was based on the addition reaction of the organolithium derivatives, derived from metal–halogen exchange of (*E*)-5-iodo-3-methyl-2-penten-1-ol to *N*-trimethylsilyl-δ-valerolactam.[2] However, the lithium–halogen exchange was problematic and could only be accomplished in low yield (10%) via 4,4′-di-*tert*-butylbiphenylide.[2]



1 Polonicumtoxin A — R = $COCH_2CH{=}CH_2$

2 Polonicumtoxin B — R = $COCH_3$

3 Polonicumtoxin C — R = H

A second approach utilized an aza-Wittig protocol for the construction of the tetrahydropyridine ring but it consisted of a seven step protocol, including the problem of protection–deprotection reactions at several stages.[2]

These two fundamental problems of a bottle-neck reaction and multistep procedure initiated us to devise an improved and alternative synthesis of the polonicumtoxins, as exemplified by the synthesis of polonicumtoxin C (**3**), the equivalent of deacylated polonicumtoxin A and B.

In this article we report two new and short approaches for the synthesis of polonicumtoxin C in overall yields of 38% (one-pot procedure) and 48% (3 step procedure).

Results and Discussion

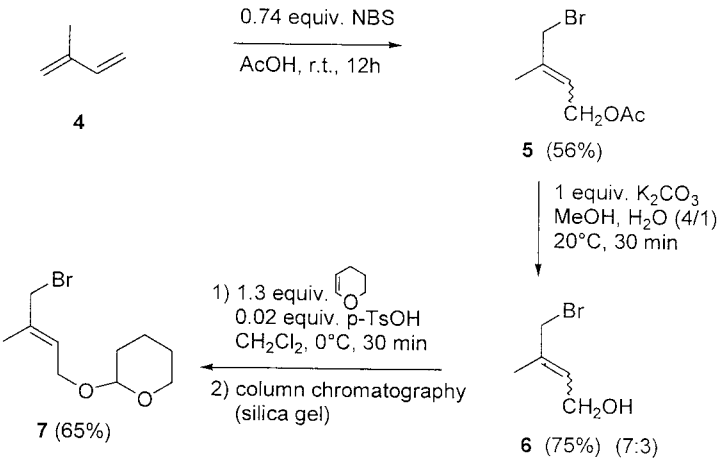
Synthesis of polonicumtoxin C (3) (route 1)

The *E*,*Z*-mixture (7:3) of 4-bromo-3-methyl-2-butene-1-ol **6** was synthesized from isoprene **4**[3] and modified according to a known procedure,[2] involving bromination with *N*-bromosuccinimide in acetic acid and subsequent cleavage of the acetate with potassium carbonate in methanol (Scheme 1). The protection of the *E*,*Z*-mixture of bromohydrins **6** by treatment with dihydropyran in the presence of *p*-TsOH in dichloromethane gave an *E*,*Z*-mixture (7:3), from which the pure *E*-bromide **7** was isolated by column chromatography on silica gel.

6-Methyl-2,3,4,5-tetrahydropyridine **9** was synthesized by treatment of 2-methyl-1-piperidine **8** with *N*-chlorosuccinimide, followed by reaction of the corresponding *N*-chloropiperidine with potassium hydroxide in methanol under reflux.

Keywords: cytotoxicity; tetrahydropyridine alkaloid; synthesis.
* Corresponding author. Tel.: +32-9-264-5951; fax: +32-9-264-6243; e-mail: norbert.dekimpe@rug.ac.be

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00702-X



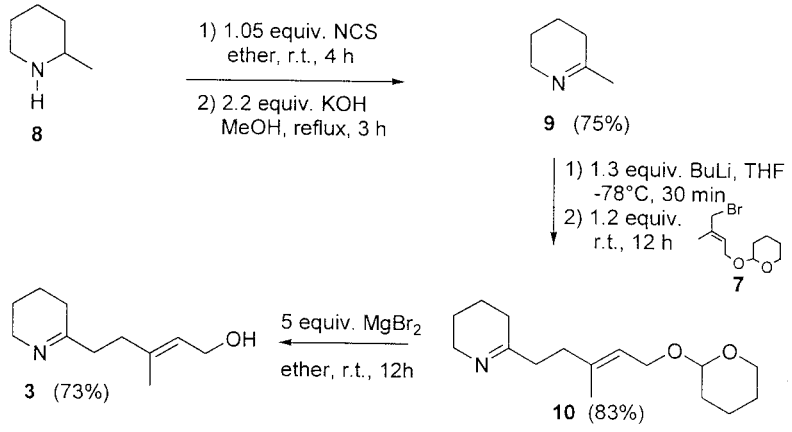
Scheme 1.

The utilization of the basic heterocyclic skeleton of the alkaloids, i.e. the tetrahydropyridine unit **9**, circumvents the previously encountered problem with the construction of the polonicumtoxin core at a latter stage in the synthesis. 6-Methyl-2,3,4,5-tetrahydropyridine **9** was deprotonated with *n*-BuLi in tetrahydrofuran at −78°C for 30 min, followed by treatment of the 1-azaallylic anion with the *E*-bromide **7** to afford γ,δ-unsaturated ketimine **10** in 83% yield. The protective tetrahydropyranyl group was removed by treatment of compound **10** with anhydrous $MgBr_2$ in ether at room temperature to give rise to the desired natural product polonicumtoxin C (**3**) in 73% yield. This product was identical in all aspects (^{1}H NMR, ^{13}C NMR, IR, MS) with the spectral data reported in the literature (see Scheme 2).[2]

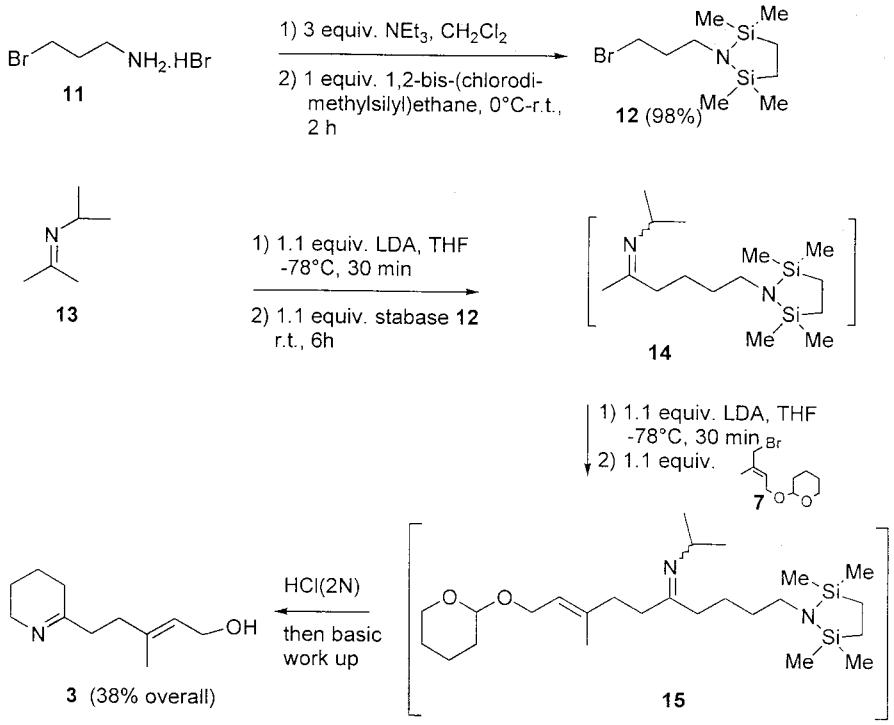
Synthesis of polonicumtoxin C (3) (route 2)

Recently, ketimines derived from simple ketones have been used conveniently for the construction of cyclic ketimines.[5,9–11] Retrosynthetically, polonicumtoxin C (**3**) can be constructed from a ketimine derived from acetone, by which two funtionalized carbon chains are attached to the α- and α′-position. Utilizing a suitable *O*- and *N*-protection, it should be possible to generate by one hydrolytic step the azaheterocycle by an intramolecular imination process and an acetal hydrolysis. The C_3-stabase protocol, i.e. α-alkylation of ketimine **13** with *N*,*N*-diprotected γ-bromopropylamine **12** (stabase),[7] subsequent *N*-deprotection and following ring closure for the construction of cyclic imines, seems to be the preferred choice for the formation of the tetrahydropyridine unit.[11] The synthesis of polonicumtoxin C (**3**) was carried out with *N*-isopropylideneisopropylamine **13** (Scheme 3). *N*-isopropylideneisopropylamine was synthesized in large scale (0.2–0.3 mol) from acetone and isopropylamine with catalytic 12 N HCl in 90% yield.[6] When synthesizing small quantities (0.1 mol) of ketimine **13**, the procedure was modified[8] by treatment of acetone with isopropylamine in the presence of titanium(IV) chloride, affording *N*-isopropylideneisopropylamine **13** in 80% yield. The *N*,*N*-disilylprotected γ-bromopropylamine **12** was synthesized from 3-bromopropylamine hydrobromide **11** by reaction with 1,2-bis-(chlorodimethylsilyl)-ethane in the presence of triethylamine [7] (Scheme 3).

Ketimine **13** was deprotonated by LDA in THF at −78°C, followed by treatment of the 1-azaallylic anion with the C_3-stabase electrophile **12** to give the intermediate δ-aminated ketimine **14**. The α′-methyl group of this intermediate **14** was sequentially deprotonated with LDA and then treated with the *E*-bromide **7** affording the intermediate functionalized ketimine **15**, which underwent removal of both the N- and O-protecting groups by treatment with HCl (2 N). Via intramolecular transimination, polonicumtoxin C (**3**) was



Scheme 2.



Scheme 3.

obtained after work up with aqueous Na_2CO_3 (5 N) in 38% overall yield, according to a one-pot procedure.

In conclusion, two convenient and straightforward synthetic pathways towards polonicumtoxin C are presented. By these methods, alkaloid **3** was either obtained in an overall yield of 38% (one-pot procedure) or 48% (3 step procedure).

Experimental

^{1}H NMR spectra (270 MHz) and ^{13}C NMR (67 MHz) were recorded with a Jeol JNM-EX 270 NMR spectrometer. Peak assignments were performed by the aid of the DEPT technique, 2D-COSY spectra and HETCOR spectra. IR spectra were measured with a Perkin Elmer model 1600 series FTIR spectrometer. Mass spectra were recorded with a Varian-MAT 112 mass spectrometer (70 eV).

***E,Z*-4-Bromo-3-methyl-1-acetoxy-2-butene 5.**[3] To a solution of 47.6 g (0.7 mol) of isoprene **4** in 300 ml of glacial acetic acid was added 92.56 g (0.52 mol) of *N*-bromosuccinimide. The reaction was stirred for 12 h at room temperature, then poured into water. The resulting mixture was extracted with CH_2Cl_2. The extract was washed with water, aqueous $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed in vacuo to give the crude product, which was distilled in vacuo to afford 82 g of an *E,Z*-mixture (7/3) of 4-bromo-3-methyl-1-acetoxy-2-butene **5** in 56% yield as a colorless oil, bp 58–61°C/0.2 mm Hg (lit.[3] 57–65°C/0.2 mm Hg). IR (NaCl): 2976, 1740 (C=O), 1654 (C=C), 1438, 1366, 1234, 1026 cm^{-1}; MS (*m/z*): no M^+, 127 (M^+-Br, 14), 85 (30), 43 (100). NMR spectral data of the *E*- and *Z*-isomers were deduced from a sample containing the *E*- and *Z*-mixture (7/3). *E*-isomer: ^{1}H NMR ($CDCl_3$): 5.73 (1H, broad t, *J*=6.9 Hz, CH=), 4.60 (2H, d, *J*=6.9 Hz, CH_2O), 3.94 (2H, s, CH_2Br), 2.06 (3H, s, OAc), 1.85 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$): 170.6 (C=O), 137.1 (C-3), 124.09 (C-2), 60.8 (C-1), 39.3 (C-4), 20.7 (CO*Me*), 14.9 (C-5). *Z*-isomer: ^{1}H NMR ($CDCl_3$): 5.73 (1H, overlap, CH=), 4.60 (2H, overlap, CH_2O), 4.01 (2H, s, H-4), 2.05 (3H, s, OAc), 1.90 (3H, s, CH_3).

***E,Z*-4-Bromo-3-methyl-2-butene-1-ol 6.**[3] To a solution of 10 g (4.8 mmol) of 4-bromo-3-methyl-1-acetoxy-2-butene **5** in 80 ml of MeOH was added a solution of 6.6 g (4.8 mmol) of K_2CO_3 in 20 ml of water at 20°C. The reaction was stirred for 30 min, then poured in water. The resulting mixture was extracted with CH_2Cl_2 and the extract was washed with water and dried ($MgSO_4$). The solvent was removed in vacuo to give the crude product, which was purified by flash chromatography (hexane/ethyl acetate, 95/5) to give 6 g of an *E,Z*-mixture (7/3) of 4-bromo-3-methyl-2-buten-1-ol **6** in 75% yield as a colorless oil. IR (NaCl): 3384 (OH), 2924, 1655 (C=C), 1449, 1378, 1093, 1008 cm^{-1}; MS (*m/z*): no M^+, 147/149 (M^+-OH, 12), 146/148 (M^+-H_2O, 4), 85 (M^+-Br, 100), 43 (96). NMR spectral data of the *E*- and *Z*-isomers were deduced from a sample containing the *E*- and *Z*-mixture (7/3). *E*-isomer: ^{1}H NMR ($CDCl_3$): 5.77 (1H, broad t, *J*=6.6 Hz, CH=), 4.20 (2H, d, *J*=6.6 Hz, CH_2O), 3.96 (2H, s, CH_2Br), 1.81 (3H, s, CH_3). *Z*-isomer: ^{1}H NMR ($CDCl_3$): 5.77 (1H, overlap, CH=), 4.20 (2H, overlap, CH_2O), 3.93 (2H, s, CH_2Br), 1.87 (3H, s, CH_3).

***E*-4-Bromo-3-methyl-1-(tetrahydro-2-pyranyloxy)-2-butene 7.**[2] Compound **7** was synthesized according to a known procedure.[2] To a solution of 1.80 g (10.9 mmol) of an *E,Z* mixture (7:3) of 4-bromo-3-methyl-2-butene-1-ol **6** in 40 ml of CH_2Cl_2 was added 1.10 g (13.08 mmol) of

dihydropyran and 28 mg (0.164 mmol) of *p*-TsOH. The reaction was stirred for 30 min at 0°C, then poured in aqueous $NaHCO_3$ (5N). The resulting mixture was extracted with CH_2Cl_2 and the extract was washed with water and dried ($MgSO_4$). The solvent was removed in vacuo to give 2.60 g of the crude product *E*,*Z*-mixture, which was separated on a silica gel column (hexane/EtOAc, 9/1) to give 1.77 g of the *E*-isomer **7** in 65% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): 5.77 (1H, t, J_1=J_2=6.9 Hz, H-2), 4.62 (1H, dd, J_1=2.6 Hz, J_2=4.3 Hz, THP acetal H), 4.26 (1H, dd, J_1=6.9 Hz, J_2=12.7 Hz, H-1), 4.05 (1H, dd, J_1=6.9 Hz, J_2=12.7 Hz, H-1), 3.97 (2H, s, H-4), 3.82–3.94 (1H, m, C*H*$_2$O), 3.48–3.55 (1H, m, C*H*$_2$O), 1.81 (3H, s, CH_3), 1.49–1.90 (6H, m, $(CH_2)_3$); ^{13}C NMR ($CDCl_3$): 135.2 (C-3), 126.9 (C-2), 97.9 (C-acetal), 63.4 (C-1), 62.1 (CH_2O), 40.1 (C-4), 30.4 (CH_2), 25.3 (CH_2), 19.3 (CH_2), 14.9 (C-5); IR (NaCl): 2942, 1655 (C=C), 1440, 1200, 1119, 1075, 1027, 906, 869 cm^{-1}; MS (*m*/*z*): no M^+, 147/149 (M^+−OTHP, 7), 85 (M^+−Br, 100), 68 (37).

6-Methyl-2,3,4,5-tetrahydropyridine 9. This compound was prepared by modification of a known procedure.[4] A mixture of 30 g (0.3 mol) of 2-methyl-1-piperidine in 30 ml of dry ether was added to a solution of 42 g (0.31 mol) of *N*-chlorosuccinimide in 300 ml of dry ether at 0°C. The reaction was stirred for 4 h at room temperature. Succinimide was removed by filtration and the filtrate reduced in volume by approximately two thirds. This resulting solution of *N*-chloropiperidine was treated with a solution of 36.6 g (0.65 mol) of KOH in 150 ml of MeOH under reflux for 3 h. The reaction mixture was poured in water and extracted with ether. The extract was washed with water, brine and dried ($MgSO_4$), after which the solvent was removed in vacuo to give the crude tetrahydropyridine **9**. Distillation in vacuo afforded 22 g of 6-methyl-2,3,4,5-tetrahydropyridine **9** in 75% yield, bp 29–30°C, 14 mm Hg (lit.[4] 135–135.5°C). ^{1}H NMR ($CDCl_3$): 3.49–3.54 (2H, m, H-2), 2.08–2.13 (2H, m, H-5), 1.90 (3H, d, *J*=1.3 Hz, CH_3), 1.51–1.68 (4H, m, H-4, H-3); ^{13}C NMR ($CDCl_3$): 167.6 (C-6), 48.7 (C-2), 29.8 (C-5), 27.1 (CH_3), 21.3 (C-3), 19.2 (C-4); IR (NaCl): 2930, 1663 (C=N), 1444, 1373 cm^{-1}; MS (*m*/*z*): 97 (M^+, 68), 96 (13), 85 (25), 69 (59), 68 (22), 42 (100).

(*E*)-6[(3-Methyl)-5-tetrahydropyranyloxy)-3-pentenyl]-2, 3,4,5-tetrahydropyridine 10. To a solution of 99 mg (1 mmol) of 6-methyl-2,3,4,5-tetrahydropyridine **9** in 5 ml of freshly distilled THF, cooled at −78°C, was added 0.5 ml (1.25 mmol) of *n*-BuLi (2.5 M in hexane). The mixture was stirred for 30 min, then 273 mg (1.1 mmol) of the *E*-bromide **7** was added. The reaction mixture was stirred for 30 min at −78°C, and gradually warmed up afterwards to room temperature and stirred for 12 h. Afterward the mixture was treated with 20 ml of NaOH (1N) and extracted with EtOAc. The extract was washed with water, and dried ($MgSO_4$). The solvent was removed in vacuo to give 340 mg of crude product, which was purified by flash chromatography on a silica gel column (CH_2Cl_2/MeOH, 9/1) to afford 220 mg of compound **10** in 83% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): 5.37 (1H, dd, J_1=6.9, J_2=6.6 Hz, H-4′), 4.61 (1H, dd, J_1=3.0 Hz, J_2=3.9, THP acetal H), 4.22 (1H, dd, J_1=6.6 Hz, J_2=12.0 Hz, H-5′), 4.01 (1H, dd, J_1=6.9 Hz, J_2=12.0 Hz, H-5′), 3.84–3.88 (1H, m, C*H*$_2$O), 3.46–3.56 (1H, m, C*H*$_2$O), 2.27 (4H, bs, H-1′, H-2′), 2.09–2.14 (2H, m, H-5), 1.69 (3H, s, H-6′), 1.53–1.85 (10H, m, $(CH_2)_3$, H-4, H-3); ^{13}C NMR ($CDCl_3$): 170.6 (C-6), 139.6 (C-3′), 122.8 (C-4′), 97.7 (C-acetal), 63.5 (C-5′), 62.2 (CH_2O), 49.0 (C-2), 39.0 (C-1′), 36.1 (C-2′), 30.6 (CH_2), 29.2 (C-5) (this carbon was reported at δ 23.9 ppm in the literature[2]), 25.4 (CH_2), 21.8 (C-4),19.5 (CH_2), 19.5 (C-3), 16.3 (C-6′); IR (NaCl): 2934, 1663 (C=N), 1655 (C=C), 1441, 1354, 1200, 1076, 1022 cm^{-1}; MS (*m*/*z*): 265 (M^+, 3), 165 (18), 164 (100), 150 (59), 136 (11), 97 (14), 85 (79).

Polonicumtoxin C (3) (route 1)

The deprotection of the THP group in compound **10** was carried out according to a known procedure.[2] To a solution of 220 mg (0.83 mmol) of **10** in 10 ml of ether was added 763 mg (4.15 mmol) of $MgBr_2$. This mixture was stirred at 15°C for 12 h, then the ether was removed in vacuo and the residue was extracted with CH_2Cl_2. The extract was washed with water, and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave 160 mg of crude product, which was purified by flash chromatography on a silica gel column (CH_2Cl_2/MeOH, 7/3) to give 110 mg of the alkaloid polonicumtoxin C (**3**) in 73% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): 5.41 (1H, t, *J*=6.9 Hz, H-4′), 4.12 (2H, d, *J*=6.9 Hz, H-5), 3.53 (2H, t, *J*=5.9 Hz, H-2), 2.70 (1H, broad s, OH), 2.25 (4H, broad s, H-1′, H-2′), 2.09–2.18 (2H, m, H-5), 1.68 (3H, s, H-6′), 1.50–1.66 (4H, m, H-4, H-3); ^{13}C NMR ($CDCl_3$): 170.9 (C-6), 138.5 (C-3′), 124.1 (C-4′), 59.1 (C-5′), 49.0 (C-2), 39.1 (C-1′), 36.1 (C-2′), 29.2 (C-5), 21.8 (C-3), 19.5 (C-4), 16.3 (C-6′); IR (NaCl): 3308 (OH), 2930, 2870, 1662 (C=N), 1655 (C=C), 1446, 1016 cm^{-1}; MS (*m*/*z*): 181 (M^+, 4), 164 (49), 164 (100), 151 (15), 150 (100), 148 (13), 136 (18), 97 (36), 55 (41).

Polonicumtoxin C (3) (route 2)

To a solution of 99 mg (1 mmol) of *N*-isopropylideneisopropylamine **13** in 5 ml of freshly distilled THF, cooled at −78°C, 0.52 ml (1.04 mmol) of LDA (2 M solution in THF/*n*-heptane) was added. Then 336 mg (1.2 mmol) of C_3-stabase **12** was added. The reaction was stirred for 30 min at this temperature, and afterwards warmed up to room temperature and stirred for 6 h. The reaction mixture was cooled again to −78°C and 0.52 ml (1.04 mmol) of LDA (2 M solution in THF/*n*-heptane) was added. The mixture was stirred for 30 min, then 273 mg (1.1 mmol) of the *E*-bromide **7** was added. The reaction mixture was stirred for 30 min, after which the mixture was warmed up to room temperature and stirred for 12 h. The mixture was treated with 20 ml of HCl (2N) for 2 h, then extracted with ether to give an organic phase and an aqueous phase. The aqueous phase was basified with 30 ml of Na_2CO_3 (5N), and subsequently extracted with CH_2Cl_2. The extract was washed with water and dried ($MgSO_4$). The solvent was removed in vacuo to give 150 mg of crude product, which was purified by flash chromatography on a silica gel column (CH_2Cl_2/MeOH, 7/3) to give 70 mg of polonicumtoxin C (**3**) in 38% yield. For the spectral data of compound **3**, see route 1.

References

1. Oshima, Y.; Minami, H.; Takano, Y.; Yasumoto, T. *Red Tides, Biology, Environmental Science and Toxicology*; Okaichi, T., Anderson, D. Y., Nemoto, T., Eds.; Elsevier: New York, 1989, pp 375–378.
2. Yamashita, M. Y.; Yasumoto, T.; Rawal, V. H. *Heterocycles* **1998**, *48* (1), 79–93.
3. Babler, J. M.; Buttner, W. J. *Tetrahedron Lett.* **1976**, *4*, 239–242.
4. Harada, K.; Mizoe, Y.; Furukawa, J.; Yamasita, S. *Tetrahedron* **1970**, *26*, 1579–1588.
5. De Kimpe, N.; Keppens, M. *J. Agric. Food Chem.* **1996**, *44*, 1515–1519.
6. Norton, D. G.; Haury, V. E.; Davis, F. C.; Mitchell, L. J.; Ballard, S. A. *J. Org. Chem.* **1954**, *19*, 1054–1065.
7. Djuric, S.; Venit, J.; Magnus, P. *Tetrahedron Lett.* **1981**, *22*, 1787–1790.
8. Armesto, D.; Bosch, P.; Gallengo, M. G.; Martin, J. F.; Ortiz, M. J.; Perez-Ossorio, R.; Ramos, A. *Org. Prep. Proced. Int.* **1987**, *19*, 181–186.
9. De Kimpe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705–3718.
10. De Kimpe, N.; Keppens, M.; Fonck, G. *J. Chem. Soc., Chem. Commun.* **1996**, 635–666.
11. De Kimpe, N.; Keppens, M.; Stevens, C. V. *Tetrahedron Lett.* **1993**, *34*, 4693–4699.