A Convenient Preparation of 7-Bromo-2*H*-1,4-benzothiazine-3,5,8(4*H*)-trione and Its Application in the Synthesis of the Conaquinone B Skeleton

Ricardo A. Tapia,* Lorena Villalobos, Cristian Salas

Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 2609441, Chile
Fax +56(2)6864744; E-mail: rtapia@puc.cl.

Received 11 May 2007

Abstract: 7-Bromo-2*H*-1,4-benzothiazine-3,5,8(4*H*)-trione was synthesized by reaction of 5-bromo-2-nitro-1,4-benzoquinone with methyl thioglycolate followed by reductive cyclization and oxidation. The Diels–Alder reaction of the product quinone with myrcene afforded the expected naphthothiazine.

Key words: natural products, quinines, Diels–Alder reactions, heterocycles, nitro compounds

Shermilamine A (**1**) and B (**2**)[1] are members of the pyridoacridines alkaloids group[2] of marine natural products that incorporate a 1,4-thiazine ring fused to the pyridoacridine system. On the other hand, conaquinones A (**3**) and B (**4**), a different type of marine natural product, have a 1,1-dioxo-1,4-thiazine ring fused to a quinone moiety[3] (Figure 1).

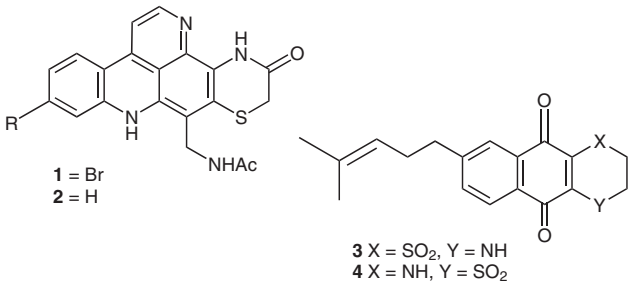


Figure 1 Structures of shermilamine A (**1**) and B (**2**) and conaquinone A (**3**) and B (**4**)

The cytotoxic activity described for compounds **1**–**4** has stimulate interest in their synthesis for the development of new types of antitumor agents. The preparation of shermilamine B (**2**) by Ciufolini et al.[4] via nitrene thermophotolysis of an aryl azide is the only synthetic work available for the total synthesis of compounds **1**–**4**.

As part of our continuing interest in biologically active heterocyclic quinones,[5] we describe here an easy access to 1,4-benzothiazine-3,5,8(4*H*)-trione **6** and the synthesis of the conicaquinone B (**4**) skeleton. Retrosynthetic analysis (Figure 2) suggested that the carbon framework of **4** should be accessible by Diels–Alder reaction of myrcene (**5**) with quinone **6**. Recently, Townsend and Jackson failed to obtain **6** from 2,5-dimethoxyaniline.[6] Taking into account that a known method to obtain 2*H*-1,4-benzothiazinones is by cyclization of (2-nitrophenylsulfanyl)acetate esters,[7] we decided to apply the reaction of methyl thioglycolate with 2-nitro-1,4-benzoquinones[8] to the preparation of a suitable precursor of **4**. Nitrobenzoquinones could be useful substrates for the synthesis of heterocyclic quinones,[9] but their use is limited by their low stability at room temperature.[10] The synthesis of the required nitrobenzoquinone **10** and of compound **6** is described in Scheme 1.

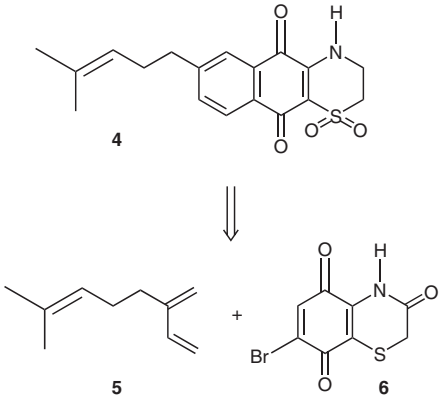
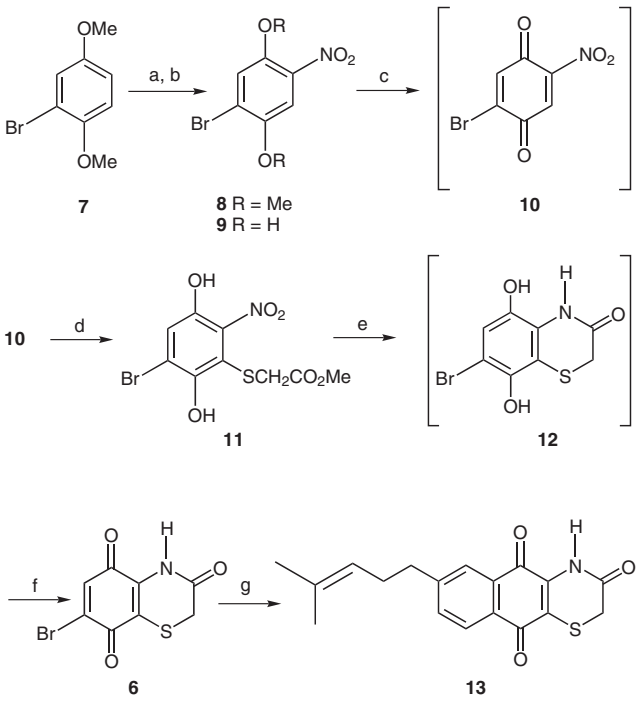


Figure 2 Retrosynthesis of conaquinone B

Our synthesis of quinone **10** began with commercially available 1-bromo-2,5-dimethoxybenzene (**7**), which was treated with nitric acid in acetic acid at room temperature to give 1-bromo-2,5-dimethoxy-4-nitrobenzene (**8**) almost quantitatively. The ^{1}H NMR spectrum of this compound showed two singlets at δ = 7.32 and 7.45 confirming that nitration occurs *para* to the bromine atom. Then, demethylation of dimethyl ether **8** with hydrobromic acid in acetic acid under reflux for four hours afforded hydroquinone **9** in 89% yield. Next, oxidation of hydroquinone **9** was carried out with nitric acid impregnated manganese(IV) oxide[11] in dichloromethane at 0–5 °C for 45 minutes; however, the product, quinone **10**, was unstable at room temperature and light-sensitive. Therefore, after oxidation of hydroquinone **9**, the solids were removed by filtration through a sintered-glass funnel under a nitrogen atmosphere and quinone **10** was trapped with methyl thioglycolate to give hydroquinone **11** in 87% yield. The optimal conditions for the reductive cyclization of methyl (2-nitrophenylsulfanyl)acetate **11** were subsequently determined. A number of methods have been used to reduce

SYNTHESIS 2007, No. 24, pp 3773–3775
Advanced online publication: 15.11.2007
DOI: 10.1055/s-2007-990895; Art ID: M03307SS



Scheme 1 *Reagents and conditions*: (a) HNO_3, AcOH, r.t., 98%; (b) HBr, AcOH, reflux, 4 h, 89%; (c) HNO_3/MnO_2, CH_2Cl_2, 0–5 °C, 45 min; (d) $HSCH_2CO_2Me$, CH_2Cl_2, r.t., 2 h, 87% from **9**; (e) Fe, EtOH, 5% HCl, reflux, 4 h; (f) Ag_2O, CH_2Cl_2, r.t., 30 min, 64% from **11**; (g) (i) **5**, toluene, reflux, 9 h, (ii) DBU, r.t., 4 h, 67%.

the aromatic nitro group, but many of them produce hydrogenolysis of carbon–halogen bonds.[12] Initially, reduction of **11** was attempted with tin(II) chloride/hydrochloric acid in refluxing ethanol because it was used to obtain benzothiazinones from (2-nitrophenylsulfanyl)acetate esters,[7] but in our case the reduction of the nitro group was not selective and hydrodehalogenation of the C–Br bond was also observed. After exploring several reaction conditions, we found that a highly selective reduction of **11** could be accomplished using iron in the presence of hydrochloric acid in refluxing ethanol for four hours. Under these conditions, the resulting hydroquinone **12** was immediately converted into 1,4-benzothiazine-3,5,8(4*H*)-trione **6** using silver(I) oxide (64% yield over two steps).

Finally, the Diels–Alder reaction of bromoquinone **6** with myrcene (**5**) was studied. It has been shown that a bromo atom on the quinone nucleus controls the regiochemistry of the Diels–Alder reaction.[13] Furthermore, high regioselectivity was observed in the reaction of 2,5-dichloro-1,4-benzoquinone with myrcene (**5**).[14] Thus, cycloaddition of bromoquinone **6** with myrcene (**5**) in toluene at reflux for 12 hours, and aromatization of the crude adduct with 1,8-diazabicyclo[5.4.0]undec-7-ene gave heterocyclic quinone **13** in 67% yield.

In summary, we have reported a convenient synthesis of the conaquinone B skeleton. The synthesis of shermilamine B analogues from 7-bromo-2*H*-1,4-benzothiazine-3,5,8(4*H*)-trione (**6**) is in progress.

Melting points were determined with a Meltemp apparatus and are not corrected. IR spectra were obtained in $CDCl_3$ on a Bruker Model Vector 22 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as reference on Bruker ACP-200 and AM-400 instruments. ^{13}C NMR spectra were recorded in $CDCl_3$ at 50 and 100 MHz. Column chromatography was performed on silica gel Merck 60 (70–230 mesh). Elemental analyses were performed on a Fison EA 1108 CHNS-O analyzer. Accurate MS measurements were determined using a Thermo Finnigan MAT 95XP spectrometer at the Facultad Ciencias Químicas y Farmacéuticas, Universidad de Chile.

1-Bromo-2,5-dimethoxy-4-nitrobenzene (8)

HNO_3 (2 mL) was added to a stirred soln of 1-bromo-2,5-dimethoxybenzene (**7**, 5.0 g, 23.04 mmol) in AcOH (10 mL) at r.t. After 15 min, H_2O (40 mL) was added and the mixture was stirred for 10 min at r.t. to give a yellow precipitate. The solid was filtered, washed with H_2O and dried at r.t. to give solely nitro isomer **8** (5.90 g, 98%); mp 150–151 °C (EtOH).

IR (KBr): 1566, 1513, 1490, 1340, 1040 cm^{-1}.

^{1}H NMR: δ = 3.90 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 7.32 (s, 1 H, H6), 7.45 (s, 1 H, H3).

^{13}C NMR: δ = 57.0 (CH_3), 57.3 (CH_3), 108.6 (CH), 118.5 (C), 119.3 (CH), 136.0 (C), 147.5 (C), 149.5 (C).

HRMS: *m*/*z* calcd for $C_8H_8BrNO_4$: 260.96367; found: 260.96296.

1-Bromo-2,5-dihydroxy-4-nitrobenzene (9)

A soln of **8** (1.5 g, 5.72 mmol) in AcOH (25 mL) and 48% aq HBr (100 mL) was heated to reflux for 4 h. After cooling, the mixture was extracted with EtOAc (4 × 20 mL) and the combined extracts were washed with H_2O and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2) to give hydroquinone **9** (1.19 g, 89%) as an orange solid; mp 115–116 °C.

IR (KBr): 3448, 1572, 1519, 1300, 1177 cm^{-1}.

^{1}H NMR: δ = 5.53 (s, 1 H, OH), 7.38 (s, 1 H, H6), 7.72 (s, 1 H, H3), 10.15 (s, 1 H, OH).

^{13}C NMR: δ = 109.9 (CH), 121.5 (C), 122.9 (CH), 133.0 (C), 145.7 (C), 146.7 (C).

HRMS: *m*/*z* calcd for $C_6H_4BrNO_4$: 232.93237; found: 232.93150.

Methyl (3-Bromo-2,5-dihydroxy-6-nitrophenylsulfanyl)acetate (11)

To a stirred soln of hydroquinone **9** (500 mg, 2.14 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C, HNO_3-impregnated MnO_2 (2.8 g) containing anhyd $MgSO_4$ (1.0 g) was added. The mixture was stirred for 45 min at 0 °C under N_2 and protected from light. The suspension was filtered through a sintered-glass funnel under N_2 and the filtrate was added to a cooled soln (0 °C) of methyl thioglycolate (300 mg, 2.8 mmol) under N_2. The solution was further stirred for 2 h and then subsequent evaporation of the solvent gave **11** as an orange oil (630 mg, 87%).

IR (KBr): 3363, 1701, 1573, 1537, 1376, 1289 cm^{-1}.

^{1}H NMR: δ = 3.79 (s, 3 H, CH_3), 3.84 (s, 2 H, CH_2), 7.50 (s, 1 H, H4), 8.84 (s, 1 H, OH), 8.95 (s, 1 H, OH).

^{13}C NMR: δ =39.1 (CH_2), 53.5 (CH_3), 95.4 (C), 120.3 (C), 126.1 (CH), 137.1 (C), 147.0 (C), 151.5 (C), 165.7 (C).

HRMS: *m*/*z* calcd for $C_9H_8BrNO_6S$: 336.92556; found: 336.92471.

7-Bromo-2*H*-1,4-benzothiazine-3,5,8(4*H*)-trione (6)

To a soln of hydroquinone **11** (500 mg, 1.49 mmol) in EtOH (15 mL) and 20% aq AcOH (6 mL) was added iron powder (10 μm. Aldrich, 363 mg, 6.5 mmol) followed by 5% aq HCl (0.5 mL). The mixture was vigorously stirred at reflux for 4 h, then cooled to r.t.,

diluted with EtOAc (80 mL), and filtered through a Celite pad. The filtrate was washed with 5% aq $NaHCO_3$ (40 mL) and H_2O (2 × 50 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (15 mL). Ag_2O (626 mg, 2.7 mmol) was added and the suspension was stirred at r.t. for 30 min and filtered. After evaporation of the solvent the residue was purified by flash chromatography to afford quinone **6** (260 mg, 64%) as an orange solid, mp 170–171 °C.

IR (KBr): 3199, 1652, 1459, 1033 cm^{-1}.

^1H NMR: δ = 3.54 (s, 2 H, CH_2), 7.31 (s, 1 H, H6), 8.10 (s, 1 H, NH).

^{13}C NMR: δ = 28.5 (CH_2), 119.5 (C), 134.2 (C), 135.4 (CH), 138.5 (C), 160.6 (C), 174.7 (C), 175.6 (C).

HRMS: *m*/*z* calcd for $C_8H_4BrNO_3S$: 272.90952; found: 272.90866.

7-(4-Methylpent-3-enyl)-2*H*-naphtho[2,3-*b*][1,4]thiazine-3,5,10(4*H*)-trione (13)

To a soln of quinone **6** (150 mg, 0.55 mmol) in toluene (10 mL) was added myrcene (**5**, 75 mg, 0.55 mmol) and the mixture was heated to reflux for 9 h. After evaporation of the solvent the residue was dissolved in CH_2Cl_2 (10 mL), DBU (84 mg, 0.55 mmol) was added, and the mixture was stirred at r.t. for 4 h. The solvent was evaporated and the residue was purified by flash chromatography ($CHCl_3$) to afford quinone **13** (120 mg, 67%) as an orange solid; mp 127.5–128 °C.

IR (KBr): 3270, 1720, 1463, 1339, 1292 cm^{-1}.

^1H NMR: δ =1.52 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 2.30–2.40 (m, 2 H, CH_2), 2.7–2.8 (m, 2 H, CH_2), 3.53 (s, 2 H, CH_2), 5.1–5.2 (m, 1 H, CH), 7.55 (dd, *J* = 7.9, 1.7 Hz, 1 H, H8), 7.9 (d, *J* = 1.7 Hz, 1 H, H6), 7.99 (d, *J* = 7.9 Hz, 1 H, H9), 8.55 (s, 1 H, NH).

^{13}C NMR: δ = 17.7 (CH_3), 25.6 (CH_3), 28.3 (CH_2), 29.2 (CH_2), 36.2 (CH_2), 122.4 (CH), 123.5 (C), 127.0 (CH), 127.2 (CH), 129.8 (C), 130.2 (C), 133.4 (C), 134.8 (CH), 135.5 (C), 149.7 (C), 161.1 (C), 179.0 (C), 180.0 (C).

HRMS: *m*/*z* calcd for $C_{18}H_{17}NO_3S$: 327.09292; found: 327.09275.

Acknowledgment

We are grateful to FONDECYT (Research Grant 1060592) for financial support.

References

(1) (a) Cooray, N. M.; Scheuer, P. J.; Parkanyi, L.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4619. (b) Carrol, A. R.; Cooray, N. M.; Poiner, A.; Scheuer, P. J. *J. Org. Chem.* **1989**, *54*, 4231. (c) Rudi, A.; Kashman, Y. *J. Org. Chem.* **1989**, *54*, 5331.
(2) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825.
(3) Aiello, A.; Fattorusso, E.; Luciano, P.; Menna, M.; Esposito, G.; Iuvone, T.; Pala, D. *Eur. J. Org. Chem.* **2003**, 898.
(4) (a) Ciufolini, M. A.; Shen, Y.-C. *Tetrahedron Lett.* **1995**, *36*, 4709. (b) Ciufolini, M. A.; Shen, Y.-C.; Bishop, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 12460.
(5) (a) Tapia, R. A.; López, C.; Morello, A.; Maya, J. D.; Valderrama, J. A. *Synthesis* **2005**, 903. (b) Tapia, R. A.; Salas, C.; Morello, A.; Maya, J. D.; Toro-Labbé, A. *Bioorg. Med. Chem.* **2004**, *12*, 2451. (c) Tapia, R. A.; Prieto, Y.; Pautet, F.; Walchshofer, N.; Fillion, H.; Fenet, B.; Sarciron, M.-E. *Bioorg. Med. Chem.* **2003**, *11*, 3407. (d) Tapia, R. A.; Alegria, L.; Pessoa, C. D.; Salas, C.; Cortés, M. J.; Valderrama, J. A.; Sarciron, M.-E.; Pautet, F. N.; Walchshofer, N.; Fillion, H. *Bioorg. Med. Chem.* **2003**, *11*, 2175.
(6) Townsend, N. O.; Jackson, Y. A. *Org. Biomol. Chem.* **2003**, *1*, 3557.
(7) Kelly, T. R.; Kim, M. H.; Curtis, A. D. M. *J. Org. Chem.* **1993**, *58*, 5855.
(8) Polgatti, V.; Valderrama, J. A.; Tapia, R. *Synth. Commun.* **1990**, *20*, 1085.
(9) Parker, K. A.; Sworin, M. *Tetrahedron Lett.* **1978**, *19*, 2251.
(10) Hammond, P. R. *J. Chem. Soc.* **1964**, 471.
(11) Cassis, R.; Valderrama, J. A. *Synth. Commun.* **1983**, *13*, 347.
(12) For a review of reductive hydrodehalogenation of organic halides, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009.
(13) (a) Lyon, M. A.; Lawrence, S.; Williams, D.; Jackson, Y. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 437. (b) Nebois, P.; Sarciron, M. E.; Bibal, B.; Bouammali, B.; Cherkaoui, O.; Pautet, F.; Pétavy, A. F.; Walchshofer, N.; Fillion, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 871. (c) Pérez, J. M.; López-Alvarado, P.; Pascual-Alfonso, E.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2000**, *56*, 4575. (d) Barker, D.; Brimble, M. A.; Do, P.; Turner, P. *Tetrahedron* **2003**, *59*, 2441. (e) Krohn, K.; Sohrab, M. H.; Florke, U. *Tetrahedron: Asymmetry* **2004**, *15*, 713. (f) Tietze, L. F.; Singidi, R. R.; Gercke, K. M. *Org. Lett.* **2006**, *8*, 5873.
(14) Miguel del Corral, J. M.; Castro, M. A.; Gordaliza, M.; Oliveira, A. B.; Gualberto, S. A.; García-Grávalos, M. D.; San Feliciano, A. *Arch. Pharm. (Weinheim, Ger.)* **2002**, *335*, 427.