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Artigo

THE SYNTHESES OF THE MARINE METABOLITES 3-BROMOVERONGIAQUINOL AND 5-MONOBROMOCAVERNICOLIN[#]

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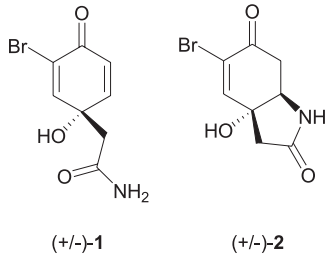
An efficient synthesis of the marine metabolite 3-bromoverongiaquinol (**1**) and the first total synthesis of 5-monobromocavernicolin (**2**), both isolated from the marine sponge *Aplysina cavernicola*, have been described based on the 1,2 addition of the lithium enolate of *N,O*-bistrimethylsilylacetamide (BSA, **4**) to 1,4-benzoquinone (**3**). Bromination and purification of the crude product on silica gel chromatography provided 3-bromoverongiaquinol (**1**) in 50% overall yield. Under alkaline conditions, the crude product of the bromination reaction was converted to 5-monobromocavernicolin (**2**) in 20% yield which was also obtained in 13% yield (25% yield based on recovered starting material) from 3-bromoverongiaquinol (**1**).

Keywords: *Aplysina cavernicola*; 3-bromoverongiaquinol and 5-monobromocavernicolin; synthesis.

INTRODUCTION

The invertebrates are the main source of biologically active natural compounds among marine organisms. Over the last 25 years, sponges have been a privileged research topic due to the large number of biologically active metabolites produced by the gender Porifera.[1] These metabolites are part of the chemical arsenal employed by these organisms against predators or to mark their territory.[2] Verongida sponges attract the attention of chemists and biologists as natural sources of unusual fatty acids,[3] steroids,[4] carotenoids[5] and aminoacids.[6] For example, from *Aplysina cavernicola* several biologically active compounds such as 3-bromoverongiaquinol (**1**)[7] and 5-monobromocavernicolin (**2**)[8] have been isolated. In 2002, compound **2** was also obtained from another marine sponge (*Suberea* aff. *praetensa*).[9]



(+/-)-**1** (+/-)-**2**

Figure 1. *Marine metabolites (+/-)-**1** and (+/-)-**2***

While 3-bromoverongiaquinol (**1**) displayed bactericidal properties against *Streptococcus faecalis* and *Bacillus subtilis*,[7] 5-monobromocavernicolin (**2**) represents the first example of a marine natural product isolated in almost racemic form (6% ee) which was shown to inhibit the growth of *Sarcina lutea*, *Bacillus subtilis*, *Alcaligenes faecalis* and *Proteus vulgaris*.[8]

Racemic 3-bromoverongiaquinol (**1**) has been previously prepared twice via anodic oxidation, albeit in very low yields (2.5 and 6.3% yield),[7,10] and the relative configuration of 5-monobromocavernicolin (**2**) was proposed based solely on spectroscopic and mass spectrometry data as no total synthesis has been reported so far.[8]

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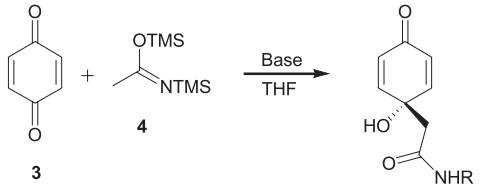
[#]This paper is dedicated to Prof. Hans Viertler

We were attracted to the synthesis of compounds **1** and **2** not only because the biological profile of 5-monobromocavernicolin (**2**) remains unexplored, but also because these two compounds may reasonably be biogenetically interconnected as (+/-)-**2** might conceivably be formed via a 1,4-addition of the amide group to the less hindered conjugated double bond in (+/-)-**1**. Therefore, it was our expectation at the onset of this work to contribute with a synthetic route to both 3-bromoverongiaquinol (**1**) and 5-monobromocavernicolin (**2**).

RESULTS AND DISCUSSION

The synthesis of compounds **1** and **2** was envisaged starting with the 1,2-addition of the lithium enolate derived from *N,O*-bistrimethylsilylacetamide (BSA, **4**) to 1,4-benzoquinone (**3**) (Scheme 1). Our first attempt was based on an analogous transformation reported by Evans and coworkers:[11] after generation of the lithium enolate of BSA (**4**) in THF at -78 ºC, the addition of 1,4-benzoquinone (**3**) was carried out at -100 ºC, to afford a mixture of silyl amide **5** (28% yield) and amide **6** (5% yield) after warm up to 0 ºC, aqueous acid treatment and purification by chromatography on silica gel (Table 1, entry 1)



3 **4**

5 R=TMS
6 R=H

Scheme 1. *Preparation of amides **5** and **6***

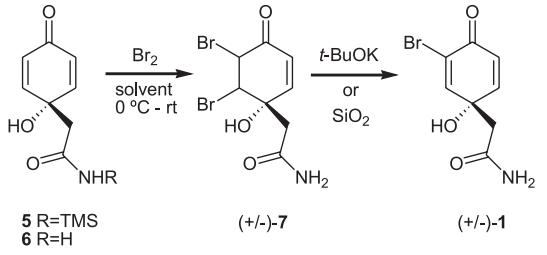
By increasing the reaction temperature to room temperature after the addition of 1,4-benzoquinone (**3**) to the lithium enolate of BSA (**4**) at -100 ºC, the combined yield of amides **5** and **6** increased to 36% with amide **6** as the major product (Table 1, entry 2). The addition of DMPU or HMPA did not prove to be beneficial (Table 1, entries 3 and 4) and the use of the sodium enolate of BSA provided neither amide **5** nor **6** (Table 1, entry 5). The best combined yield of amides **5** and **6** (56%) was achieved by employing 2.0 equiv. of the lithium enolate of BSA and reaction temperature ranging from -100 ºC to rt,

which afforded amide **6** as the major product in 38% yield accompanied by silyl amide **5** in 18% yield, after column chromatography on silica gel (Table 1, entry 6).

Table 1. Reaction conditions and yields for amides **5** and **6**

Entry	Base	BSA (equiv.)	Temperature	Additive	**5** (%)	**6** (%)
1	LDA	1.0	-100 ºC to 0 ºC	-	28	5
2	LDA	1.0	-100 ºC to rt	-	4	32
3	LDA	1.0	-100 ºC to rt	DMPU	6	25
4	LDA	1.0	-100 ºC to rt	HMPA	5	12
5	NaHMDS	1.0	-100 ºC to rt	-	-	-
6	LDA	2.0	-100 ºC to rt	-	18	38

We next investigated the bromination reaction of amides **5** and **6** in order to achieve the preparation of 3-bromoverongiaquinol (**1**). Despite being only partially soluble in $CHCl_3$, each amide reacted with bromine at 0 ºC to rt via the dibromo derivative (+/-)-**7**, as revealed by ^{1}H-NMR data of the crude mixture, to afford, after column chromatography on silica gel, 3-bromoverongiaquinol (**1**) in reasonable overall yield (67%) in both cases. Acetonitrile proved to be the best solvent and, after the same sequence of steps, both amides **5** and **6** provided 3-bromoverongiaquinol (**1**) in 89% overall yield (Scheme 2).

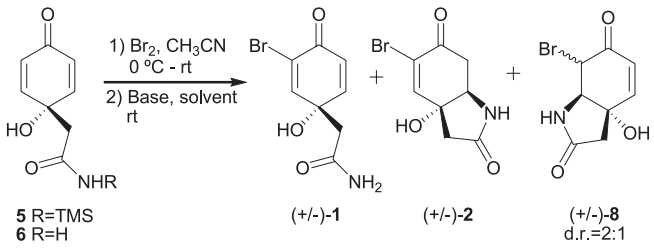


Scheme 2. *Synthesis of (+/-)-3-bromoverongiaquinol (**1**)*

To explore the preparation of 5-monobromocavernicolin (**2**) directly from silyl amide **5** and amide **6** (Scheme 3), their bromination products were treated with LDA but (+/-)-5-monobromocavernicolin (**2**) was isolated in low yield both from silyl amide **5** and from amide **6** (Table 2, entries 1 and 2). The same poor result was observed when (+/-)-**6** was treated with NaHMDS in THF (Table 2, entry 3). When the bromination products of amides **5** and **6** were treated with *tert*-BuOK, only (+/-)-**1** was obtained in 74% yield from both amides.

In all these attempts to obtain (+/-)-**2** via the bromination-dehydrobromination-1,4-addition sequence the main product was always (+/-)-3-bromoverongiaquinol (**1**). These results clearly pointed out that the use of a strong base was not appropriate to promote the requisite 1,4-addition, probably due to the reversible nature of this addition under strongly basic conditions. Then, we turned our attention to the use of DBU, a weaker base which is known to promote dehydrobromination to generate unsaturated ketones.[12] In fact, after bromination of silyl amide (+/-)-**5** in CH_3CN at 0 ºC, treatment of the crude product with 1.0 equiv. of DBU provided (+/-)-**2** in 20% overall yield (Table 2, entry 4) with (+/-)-**1** as the major product (47% yield).

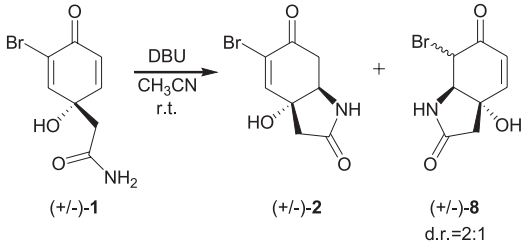
Finally, we explored the formation of 5-monobromocavernicolin (**2**) from 3-bromoverongiaquinol (**1**) by treating the latter compound in CH_3CN with 1.0 equiv. of DBU (Scheme 4). The reaction provided (+/-)-**2**, in 13% yield (25% based on recovered starting material), and its regioisomer (+/-)-**8** (25% yield). In spite of the competitive formation of (+/-)-**8**, this result demonstrates the feasibility of the conversion of (+/-)-**1** to (+/-)-**2** under basic conditions.



Scheme 3. *Synthesis of (+/-)-5-monobromocavernicolin (**2**) and lactam (+/-)-**8***

Table 2. Cyclization products derived from amide **5** and **6**

Entry	R	Base (equiv.)	Solvent	(+/-)-**1** (%)	(+/-)-**2** (%)	(+/-)-**8** (%)
1	H	LDA (1.0)	THF	45	4	22
2	TMS	LDA (3.0)	THF	23	5	12
3	H	NaHMDS (1.0)	THF	55	3	6
4	TMS	DBU (1.0)	CH_3CN	47	20	10



Scheme 4. *Synthesis of (+/-)-5-monobromocavernicolin (**2**) from 3-bromoverongiaquinol (**1**)*

Synthetic 5-monobromocavernicolin (**2**) displayed spectroscopic (IR, ^{1}H- and ^{13}C-NMR) and mass spectrum data identical to those reported by Pietra and coworkers[8] for natural 5-monobromocavernicolin (**2**), thus confirming the assignment of its relative configuration.

EXPERIMENTAL

Instrumentation

^{1}H-RMN and ^{13}C-RMN were record on a Varian Gemini instrument operating at 300 and 75 MHz, respectively, or on a Varian Inova instrument operating at 500 and 125 MHz, respectively. Infrared spectra were obtained with a Thermo Nicolet IR-200 instrument. Mass spectra were measured on a VG Autospec instrument using EI technique at 70 eV or on a QTof Ultima Waters using ESI technique.

2-(1-Hydroxy-4-oxo-2,5-cyclohexadienyl)-*N*-trimethylsilyl acetamide (5) / 2-(1-hydroxy-4-oxo-2,5-ciclohexadienyl) acetamide (6)

To a flask equipped with a magnetic stirring bar, under argon atmosphere and at -78 ºC was added diisopropylamine (0.20 mL, 1.41 mmol) and THF (12.0 mL). To this solution was added *n*-BuLi (2.35 M soln. in hexanes, 0.60 mL, 1.41 mmol) and after stirring 5 min at -78 ºC, *N,O*-bistrimethylsilylacetamide (BSA, 0.70 mL, 2.82 mmol) was added and stirring was maintained for 30 min at the same temperature. The reaction mixture was cooled to -100 ºC for the addition of a soln. of 1,4-benzoquinone (0.152 g, 1.41 mmol) in THF (5.0 mL) and the reaction mixture was kept at -78 ºC for 3 h. The reaction

mixture was warmed up to rt, satd. NH_4Cl soln. was added and after drying over $MgSO_4$ and filtration through a pad of Celite, the solvent was removed under reduced pressure. After column chromatography on silica gel (ethyl acetate as eluent), **5** (0.062 g, 0.26 mmol) was obtained in 18% yield as a white solid (mp 101-103 ºC) and **6** (0.091 g, 0.54 mmol) in 38% yield as a white solid (mp 114-115 ºC).

Analytical data for 2-(1-Hydroxy-4-oxo-2,5-cyclohexadienyl)-N-trimethylsilyl acetamide (**5**): IR (neat, cm^{-1}): 3359, 2952, 1682, 1404, 1072 and 845. ^{1}H-NMR [300 MHz, $(CD_3)_2CO$)]: δ7.19 (2H, d, *J* 10.3 Hz), 6.88 (1H, br s), 6.40 (1H, br s), 6.16 (2H, d, *J* 10.3 Hz), 2.58 (2H, s) and 0.13 (9H, s). ^{13}C-NMR [75 MHz, $(CD_3)_2CO$)]: δ 185.0, 170.0, 151.6, 127.7, 70.5, 48.8 and 1.5. HRMS (70 eV, *m/z*): calcd. for $C_{11}H_{17}NO_3Si$ - $M^{\bullet+}$ 239.09777; found: 239.09711.

Analytical data for 2-(1-hydroxy-4-oxo-2,5-ciclohexadienyl) acetamide (**6**): IR (neat, cm^{-1}): 3359, 2929, 1660, 1622, 1402 and 1032. ^{1}H-NMR [300 MHz, $(CD_3)_2CO$)]: δ 7.23 (1H, br s), 7.04 (2H, d, *J* 10.3 Hz), 6.80 (1H, br s), 6.10 (1H, d, *J* 10.3 Hz), 5.90 (1H, s) and 2.61 (2H, s). ^{13}C-NMR [75 MHz, $(CD_3)_2CO$)]: δ 184.2, 172.1, 150.4, 126.6, 67.3 and 43.4. HRMS (70 eV, *m/z*): calcd. for $C_8H_9NO_3$ - $M^{\bullet+}$, 167.05824; found: 167.04752.

(+/-)-3-Bromoverongiaquinol (1)

A soln. of silyl amide **5** (0.022 g, 0.09 mmol) in acetonitrile (0.80 mL) was cooled to 0 ºC when a 0.1 M soln. of bromine in $CHCl_3$ (0.90 mL, 0.090 mmol) was added. The reaction mixture was stirred at rt for 30 min and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate as eluent) to afford (+/-)-**1** (0.019 g, 0.08 mmol) in 89% yield as a yellowish oil. An analogous procedure provided (+/-)-**1** from amide (+/-)-**6**. IR (film, cm^{-1}): 3348, 1668, 1406, 1030, 964 and 827.

^{1}H-NMR [500 MHz, $(CD_3)_2CO$]: δ 7.56 (1H, d, *J* 2.6 Hz), 7.20 (1H, br s), 7.12 (1H, dd, *J* 10.1 and 2.7 Hz), 6.70 (1H, br s), 6.25 (1H, d, *J* 10.1 Hz), 5.96 (1H, s) and 2.71 (2H, d, *J* 1.1 Hz). ^{13}C-NMR [125 MHz, $(CD_3)_2CO$)]: δ 178.1, 172.1, 151.9, 151.8, 125.8, 123.5, 71.0 and 43.9. HRMS (70 eV, *m/z*): calcd. for $C_8H_8NO_3Br$ - $M^{\bullet+}$, 244.96876; found: 244.96901.

(+/-)-5-monobromocavernicolin (2) and 7-Bromo-3a-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-2,6-indoledione (8)

Method A: To a soln. of (+/-)-**5** (0.015 g, 0.06 mmol) in acetonitrile (0.80 mL) cooled to 0 ºC was added dropwise a 0.1 M soln of bromine in $CHCl_3$ (0.60 mL, 0.06 mmol). The reaction mixture was let to stir 30 min at rt when the solvent was removed under reduced pressure to provide a brown solid residue, which was dissolved in CH_3CN (6.0 mL) and treated with DBU (9.0 µL, 0.06 mmol). After stirring 12 h at rt, a satd. soln. of NH_4Cl was added, the mixture was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (1:9 hexanes/ethyl acetate as eluent) to afford (+/-)-**2** (2.9 mg, 0.012 mmol) in 20% yield as a colorless solid (mp 184-185 ºC) together with (+/-)-**1** (6.8 mg, 0.028 mmol) and (+/-)-**8** (1.4 mg, $5.7x10^{-3}$ mmol).

Method B: To a soln. of (+/-)-**1** (6.8 mg, 0.028 mmol) in acetonitrile (3.0 mL) was added DBU (4.2 µL, 0.028 mmol). After stirring 12 h at rt, a satd. soln. of NH_4Cl was added and the mixture was treated with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (1:9 hexanes/ethyl acetate as eluent) to afford (+/-)-**2** (0.9 mg, 3.7 $x10^{-3}$ mmol) in 13% yield [25% yield based on recovered (+/-)-**1**] as a colorless solid and (+/-)-**8** (1.6 mg, 6.5 $x10^{-3}$ mmol) in 23% yield.

Analytical data for (+/-)-5-monobromocavernicolin (**2**): IR (neat, cm^{-1}): 3438, 2922, 2852, 1689, 1410, 1331, 1051, 1026, 1001, 825 and 764. ^{1}H-NMR [300 MHz, $(CD_3)_2CO$]: δ 7.29 (1H, br s), 7.09 (1H, br s), 5.38 (1H, br s), 4.14 (1H, br t), 3.04 (1H, dd, *J* 16.4 and 4.8 Hz), 2.68 (1H, d, *J* 16.7 Hz) and 2.58 (1H, d, *J* 16.7 Hz). ^{1}H-NMR [500 MHz, CD_3OD]: δ 7.27 (1H, br s), 4.08 (1H, br t), 3.05 (1H, dd, *J* 16.5 and 4.7 Hz), 2.82 (1H, dd, *J* 16.5 and 6.4 Hz), 2.75 (1H, d, *J* 17.0 Hz) and 2.68 (1H, d, *J* 17.0 Hz). ^{1}H-NMR [500 MHz, $(CD_3)_2SO$)]: δ 7.95 (1H, br s), 7.28 (1H, br s), 6.28 (1H, br s), 3.88 (1H, br t), 2.92 (1H, dd, *J* 16.2 and 4.3 Hz), 2.71 (1H, dd, *J* 16.8 and 6.1 Hz), 2.60 (1H, d, *J* 16.5 Hz) and 2.45 (1H, d, *J* 16.5 Hz). ^{13}C-NMR [125 MHz, CD_3OD]: δ 190.7, 177.1, 150.7, 125.5, 76.4, 61.9, 45.6 and 41.6. ^{13}C-NMR [125 MHz, $(CD_3)_2SO$)]: δ 189.0, 172.8, 150.1, 122.5, 74.2, 58.7, 43.7 and 39.8. HRMS (ESI, *m/z*): calcd. for $C_8H_9NO_3Br$ - MH^+, 245.9766; found: 245.9742.

Analytical data for 7-Bromo-3a-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-2,6-indoledione (**8**): IR (film, cm^{-1}): 3269, 2979, 2925, 1685, 1396, 1244, 1097 and 1049. ^{1}H-NMR (300 MHz, $(CD_3)_2CO$): δ [7.71 (br s) and 7.23 (br s) 1H], 7.01 (d, *J* 10.3 Hz) and 6.88 (d, *J* 10.3 Hz), 1H], [6.16 (d, *J* 10.3 Hz) and 6.11 (d, *J* 10.3 Hz) 1H], [5.42 (br s) and 5.33 (br s), 1H], [5.12 (d, *J* 4.0 Hz) and 5.08 (d, *J* 9.9 Hz), 1H], [4.42 (br d, *J* 4.0 Hz) and 4.16 (dd, *J* 10.1 and 1.5 Hz) 1H], [2.87 (d, *J* 16.8 Hz) and 2.70 (d, *J* 16.8 Hz), 1H] and [2.61 (d, *J* 16.8 Hz) and 2.47 (d, *J* 16.8 Hz), 1H]. ^{13}C-NMR [75 MHz, $(CD_3)_2CO$)]: δ 190.0, 189.5, 173.8, 173.5, 149.7, 148.7, 125.8, 125.7, 75.0, 73.5, 69.6, 65.2, 58.5, 54.3, 45.4 and 43.5.

CONCLUSIONS

In this work, we have described the preparation of (+/-)-3-bromoverongiaquinol (**1**) in 50% overall yield from 1,4-benzoquinone (**3**), a more efficient approach than the one previously described in the literature. The first total synthesis of (+/-)-5-monobromocavernicolin (**2**) in 11% overall yield from 1,4-benzoquinone (**3**) was also described, thus confirming the relative configuration assigned by Pietra and coworkers. Additionally, it was demonstrated that 5-monobromocavernicolin (**2**) can be prepared in 13% yield (or 25% based on recovered starting material) from 3-bromoverongiaquinol (**1**) giving support to a conceivable biogenetic origin of (+/-)-**2** from (+/-)-**1**.

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