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Tetrahedron Letters 49 (2008) 2258–2261
Tetrahedron Letters

# Synthetic studies on basidifferquinones: the first synthesis of (±)-basidifferquinone C

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Received 9 January 2008; revised 1 February 2008; accepted 5 February 2008
Available online 8 February 2008

**Abstract**

Basidifferquinones, isolated from *Streptomyces* sp., are potent inducers for fruiting-body formation of a basidiomycete *Polyporus arcularius*. Construction of the basic framework of basidifferquinones and the first synthesis of (±)-basidifferquinone C were accomplished by starting from 3,5-dihydroxy-2-naphthoic acid.


*Keywords:* Anthraquinones; Fruiting-body inducer; *Polyporus arcularius*; Diels–Alder reaction

The fruiting-body development in basidiomycetes is the most dramatic expression of differentiation and morphogenesis among fungi, and is known to be induced by not only environmental and physical stimuli but also various chemicals.[1] In 1990, basidifferquinone was isolated from the culture medium of *Streptomyces* sp. B-412 by Azuma, Beppu and their co-workers as an inducer for fruiting-body formation in *Polyporus* (*Favolus*) *arcularius*.[2] Three years later, they also reported the isolation of two other basidifferquinone relatives.[3] Thus, the originally isolated basidifferquinone was renamed basidifferquinone A (BDQ A, **1**), and the others were named basidifferquinone B (BDQ B, **2**) and basidifferquinone C (BDQ C, **3**), respectively, as shown in Figure 1.[3] Although BDQs seem to be conventional anthraquinone derivatives at a glance, the basic framework of basidifferquinones was surprisingly quite rare in not only natural but also artificial products. To the best of our knowledge, the most structurally similar natural product may be mumbaistatin (**4**) isolated from *Streptomyces* sp. DSM 11641 as a glucose-6-phosphate translocase inhibitor.[4] Only a few studies toward the

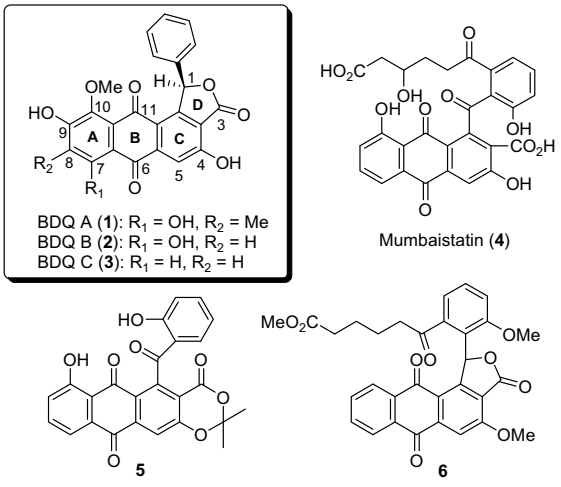


Fig. 1. Structures of BDQs and their related compounds.

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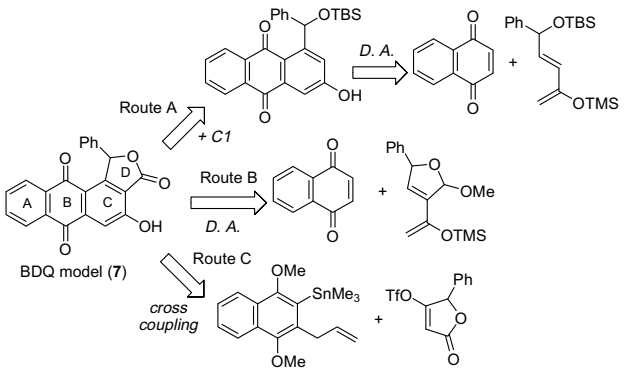
doi:10.1016/j.tetlet.2008.02.011

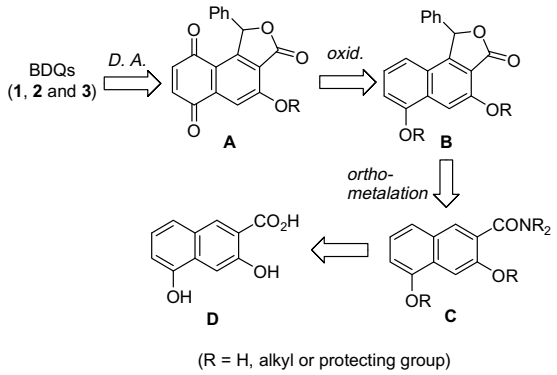
synthesis of **4** have been reported by two independent groups,[5] and they were successful in synthesizing the advanced derivatives, such as **5**[5c] and **6**,[5d] respectively. However, total synthesis of **4** has not yet been reported. On the other hand, no synthetic studies on BDQs have so far been disclosed despite their interesting biological activities. These facts may suggest that the construction of the basic framework of these compounds is much more challenging than expected. We became interested in the fascinating biological activity and unique structure of BDQs and initiated our studies toward their synthesis. Herein, we report the first synthesis of (±)-**3**.

We have been engaged in the synthetic studies on BDQs for a long time. Scheme 1 shows some of our previously attempted strategies for the A-ring simplified BDQ model compound (**7**).[6] In route A, the key Diels–Alder reaction proceeded, but the critical installation of one carbon atom corresponding to C3 was unsuccessful. However, in contrast, the key Diels–Alder reaction could not be performed in route B. In route C, the key cross coupling was not successful. Because the key features of all these strategies were the construction and functionalization of C-ring portion, these failures led us to the conclusion that C-ring construction was no easy task. In other words, we learned that we should circumvent the difficulty of C-ring construction.

We then, therefore, designed a new synthetic plan, which was quite simple as illustrated in Scheme 2 based on our previous failures. The target compounds (**1–3**) should be prepared by Diels–Alder reaction between the naphthoquinone derivative **A** and the properly functionalized dienes. For the synthesis of the key intermediate **A**, an appropriate precursor should be **B**, because the oxidation of **B** to **A** was basically feasible. To construct the lactone portion of **B**, *ortho*-lithiation[7] of intermediate **C** and the subsequent trapping with benzaldehyde was one of the reliable methods. Amide **C** might be prepared from the commercially available starting material **D**. The crucial point of this plan was to circumvent the difficulty of C-ring construction, as mentioned above, by starting from **D**.



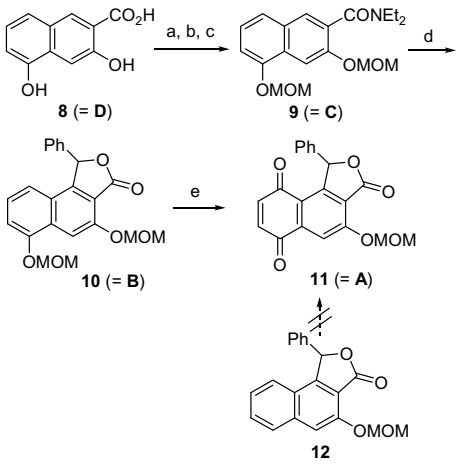

Scheme 1. Previously attempted synthetic plans for BDQs.



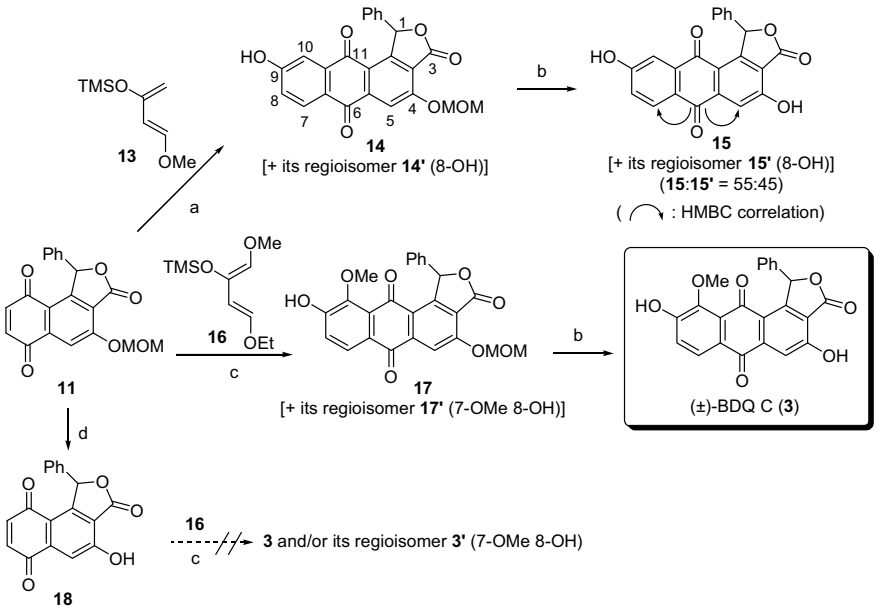

Scheme 2. Synthetic plan for BDQs.

Our starting material was the commercially available 3,5-dihydroxy-2-naphthoic acid **8** (=**D**) as illustrated in Scheme 3. This was converted to the corresponding protected amide **9** (=**C**) by the conventional 3 steps: MOM protection (82%), hydrolysis (92%), and amidation (89%). The *ortho*-lithiation[7] of **9** was performed by treatment with *n*-BuLi in the presence of TMEDA, and the generated 1-lithio intermediate was trapped with benzaldehyde to give the desired adduct, which was then immediately heated in refluxing toluene to afford the corresponding lactone **10** (=**B**) in 70% yield (based on the recovered SM). Although the reaction conditions were not yet fully optimized, *n*-BuLi was found to be better than *s*-BuLi as a base. The oxidation of **10** was successfully executed by treatment with CAN to give the corresponding naphthoquinone **11**[8] (=**A**) in quantitative yield. It was noteworthy that the oxidation of **12**[9] to **11** was unsuccessful in spite of all our efforts.

With naphthoquinone **11** in hand, we then turned to the next key step, Diels–Alder reaction. As shown in Scheme 4, we first tried to carry out Diels–Alder reaction between **11** and Danishefsky–Kitahara diene **13**.[10] With regard to the reaction procedure, we followed that of Tietze et al.,[11]




Scheme 3. Synthesis of naphthoquinone **12**. Reagents and conditions: (a) MOMCl, $^{i}Pr_2NEt$, DMF (82%); (b) KOH, aq MeOH (92%); (c) EtOCOCl, $Et_3N$, THF, then $Et_2NH$ (89%); (d) (i) *n*-BuLi, TMEDA, THF −78 °C, then PhCHO; (ii) toluene reflux (70% based on the recovered SM); (e) CAN, aq $CH_3CN$ (quant.).




Scheme 4. Synthesis of (±)-**3**. Reagents and conditions: (a) (i) $CH_2Cl_2$, rt; (ii) $SiO_2$, THF, rt; (iii) $K_2CO_3$, aq THF, rt (39%; **14**:**14**′ = 55:45); (b) *p*-TsOH, MeOH, $CHCl_3$ (99% for **15**/**15**′; 95% for **3**); (c) (i) $CH_2Cl_2$, rt then $SiO_2$; (ii) $K_2CO_3$, aq THF, rt (26%; **17**:**17**′ = 1:1); (d) dil HCl, THF (95%).

because theirs seemed to be appropriate for the purpose of synthesizing the more oxygenated compounds such as BDQs. Diels–Alder reaction between **11** and **13** underwent in $CH_2Cl_2$ at room temperature to give the adducts, which were then successively treated with $SiO_2$ in THF and then $K_2CO_3$ in aq THF to afford the desired anthraquinones **14** and its regioisomer **14**′ (8-OH isomer) in 39% yield as an inseparable mixture. The ratio of **14**:**14**′ was estimated to be 55:45 based on the NMR analysis. Although the isolated yield and the regioselectivity were quite moderate, we were successful in constructing the basic framework of BDQs. A mixture of **14** and **14**′ was then converted to a mixture **15** and **15**′ (55:45) in 99% yield by the deprotection of MOM group. The structures of **15**/**15**′ were confirmed by HMBC spectroscopy as depicted in Scheme 4. The overall yield of a mixture of **15** and **15**′ was 19% in 7 steps based on the starting material **8**. We can say that the obtained **15** is *10-demethoxy-BDQ C*.

We turned our attention to the synthesis of (±)-BDQ C (**3**). After the preparation of diene **16**,[11,12] the naphthoquinone **11** was subjected to Diels–Alder reaction with **16** and subsequently worked up in a similar manner. Although the desired product **17** and its regioisomer **17**′ (7-OMe 8-OH isomer) were obtained, the isolated yield and the regioselectivity became worse compared to the case with Danishefsky's diene **13**. After several attempts of trial and error, we managed to get a mixture of **17** and **17**′ in 26% yield (**17**:**17**′ = 1:1).[13] It was to be noted that not only the isolated yield (17–26%) but also the ratio of **17**:**17**′ (1:1–1:2) was considerably fluctuated depending on certain unknown factors. The regiochemistries of **17**/**17**′ were tentatively estimated on the basis of the NMR spectral similarities between **17**/**17**′ and **14**/**14**′.[14] The obtained mixture of **17** and **17**′ was purified by preparative TLC to give pure **17**, which was then deprotected by treatment with *p*-TsOH to give (±)-**3** in 95% yield. The various spectral data of the synthetic (±)-**3** were in good accord with those of the natural product.[15] The overall yield was 6% in 7 steps based on the starting material **8**. Although there still remained room for improvement in the key Diels–Alder reaction,[16] we were successful in the first and straightforward synthesis of (±)-BDQ C (**3**).

In conclusion, we could accomplish the construction of the basic framework of BDQs and the first synthesis of (±)-BDQ C (**3**) by employing Diels–Alder strategy. Our established synthetic route is quite simple and straightforward, and will be also applicable for the synthesis of other BDQs and their derivatives. Further studies toward the improvement of the key Diels–Alder reaction and the synthesis of other BDQs are now ongoing in our laboratory.

## Acknowledgments

We thank Drs. Tsunehiro Nishi, Udo Grieser, and Shinichi Takanashi for their contributions in the early phase of this work. This work was financially supported in part by Otsuka Chemical Co., Ltd.

## References and notes

1. For examples: (a) Uno, I.; Ishikawa, T. *J. Bacteriol.* **1973**, *113*, 1240–1248; (b) Kawai, G.; Ikeda, Y. *Biochim. Biophys. Acta* **1982**, *719*, 612–618; (c) Murao, S.; Hayashi, H.; Tarui, N. *Agric. Biol. Chem.* **1984**, *48*, 1669–1671; (d) Hayashi, H.; Tarui, N.; Murao, S. *Agric. Biol. Chem.* **1985**, *49*, 101–105; (e) Magae, Y.; Nishimura, T.; Ohara, S. *Mycol. Res.* **2004**, *109*, 374–376; (f) Magae, Y.; Ohara, S. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 1979–1982.
2. (a) Azuma, M.; Yoshida, M.; Horinouchi, S.; Beppu, T. *Agric. Biol. Chem.* **1990**, *54*, 1441–1446; (b) Azuma, M.; Hori, K.; O-hashi, Y.;

Yoshida, M.; Horinouchi, S.; Beppu, T. *Agric. Biol. Chem.* **1990**, *54*, 1447–1452.
3. Azuma, M.; Yoshida, M.; Horinouchi, S.; Beppu, T. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 344–345.
4. Vertesy, L.; Kurz, M.; Paulus, E. F.; Schummer, D.; Hammann, P. *J. Antibiot.* **2001**, *54*, 354–363.
5. (a) Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H.-G. *J. Org. Chem.* **2002**, *67*, 9248–9256; (b) Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H.-G. *Tetrahedron* **2003**, *59*, 3201–3217; (c) Krohn, K.; Diederichs, J.; Riaz, M. *Tetrahedron* **2006**, *62*, 1223–1230; (d) Sucunza, D.; Dembkowski, D.; Neufeind, S.; Velder, J.; Lex, J.; Schmalz, H.-G. *Synlett* **2007**, 2569–2573; (e) Lee, T. S.; Das, A.; Khosla, C. *Bioorg. Med. Chem.* **2007**, *15*, 5207–5218.
6. These results are unpublished.
7. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933 and references cited there in.
8. Properties of **11**: Red-orange powder; mp = 167–168 °C; IR $\nu_{max}$ (Nujol) 1760 (C═O), 1660 (C═O) $cm^{-1}$; HRFABMS $[M+H]^+$ obs 351.0868 calcd for $C_{20}H_{15}O_6$ 351.0869; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta = 3.52$ (3H, s), 5.46 (2H, q-like, $J = 6.6$ Hz), 6.73 (1H, d, $J = 10.2$ Hz), 6.76 (1H, s), 6.87 (1H, d, 10.2 Hz), 7.11–7.26 (5H, m), 7.86 (1H, s); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta = 57.2$, 83.2, 95.2, 112.9, 119.3, 120.4, 128.0, 128.5, 129.1, 135.2, 137.9, 138.4, 139.1, 152.8, 159.6, 165.9, 182.4, 183.7.
9. The naphthofuranone **12** was prepared from the commercially available 3-hydroxy-*N*-(2-methylphenyl)-2-naphthamide in two steps.
10. (a) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7809; (b) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406.
11. Tietze, L. F.; Güntner, C.; Gericke, K. M.; Schuberth, I.; Bunkoczi, G. *Eur. J. Org. Chem.* **2005**, 2459–2467.
12. Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 2642–3659.
13. A mixture of **11** (45 mg, 0.13 mmol) and **16** (0.10 ml, 0.43 mmol) in $CH_2Cl_2$ (5 ml) was stirred at rt for 2 h under Ar. After treating with $SiO_2$ (2 g) for 30 min, the reaction mixture was filtered and concentrated. The residue was treated with $K_2CO_3$ (20 mg, 0.15 mmol) in aq THF (50 vol %; 4 ml) for 30 min, diluted with $H_2O$ and extracted with EtOAc. The organic layer was washed with $H_2O$ and brine, dried ($MgSO_4$), and concentrated. The residue was purified by $SiO_2$ column chromatography to give a mixture of **17** and **17′** (15 mg; 26%).
14. The structures of **17/17′** were unambiguously confirmed by the fact that **17** could be converted to (±)-**3**.
15. Properties of synthetic (±)-**3**: Orange-yellow powder; mp = >250 °C (decomp.); IR $\nu_{max}$ (Nujol) 1730 (C═O), 1660 (C═O) $cm^{-1}$; HRFABMS $[M+H]^+$ obsd 403.0811 calcd for $C_{23}H_{15}O_7$ 403.0818; $^1H$ NMR (300 MHz, $C_5D_5N$) $\delta = 3.53$ (3H, s), 7.22–7.33 (4H, m), 7.43 (1H, d, $J = 8.4$ Hz), 7.53–7.56 (2H, m), 8.13 (1H, s), 8.21 (1H, d, $J = 8.4$ Hz); $^{13}C$ NMR (75 MHz, $C_5D_5N$) $\delta = 61.0$, 84.1, 116.2, 117.9, 120.9, 121.7, 125.9, 126.6, 127.3, 128.8, 128.9 (two coincident peaks), 137.7, 140.4, 148.6, 154.4, 159.5, 164.1, 168.5, 181.3.181.9.
16. There were two options for improving the regioselectivity of the key Diels–Alder reaction. One was Lewis acid-mediated Diels–Alder reaction, because Lewis acid could often reverse the regioselectivity in Diels–Alder reaction and generated products that would not otherwise be observed in a simple non-catalyzed reaction.[17,18] Thus, the following Lewis acids, $BF_3{\cdot}OEt_2$, $Et_2AlCl$, $Sc(OTf)_3$ and $Yb(OTf)_3$, were tested as an additive.[19] However, despite all our efforts, only a trace amount or none of **17/17′** was obtained. These unfavorable poor yields were probably due to the intrinsic instabilities of substrates, intermediates and/or products in the presence of Lewis acid. The other option was the deprotection of MOM group of **11**, because Tietze and his co-workers have reported a complete reversal of the regioselectivity in Diels–Alder reaction between **16** and juglone or its methyl ether depending on the protection of a phenolic hydroxyl group.[11,18b] Thus, hydroxynaphthoquinone **18** was prepared by the deprotection of MOM group of **11** (Scheme 4). However, surprisingly, the Diels–Alder reaction between **16** and **18** gave no desired adducts (**3/3′**) at all.
17. For Lewis acid-mediated Diels–Alder reaction: (a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436–4437; (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 339–345; (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.
18. For examples: (a) Dickinson, R. A.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1972**, *50*, 2377–2380; (b) Beckman, R. K.; Dolak, T. M.; Culos, K. O. *J. Am. Chem. Soc.* **1978**, *100*, 7098–7100; (c) Das, J.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308–3319; (d) Tou, J. S.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 5012–5014; (e) Arséniyadis, S.; Rodriguez, R.; Spanevello, R.; Camara, J.; Thompson, A.; Guittet, E.; Ourisson, G. *Tetrahedron* **1992**, *48*, 1255–1262; (f) Carreño, M. C.; Ruano, J. L. G.; Remor, C. Z.; Urbano, A. *Tetrahedron: Asymmetry* **2000**, *11*, 4279–4296.
19. The reaction procedure was also analogous to that of Tietze's[11] except for being performed at −78 °C. As an additive, $BF_3{\cdot}OEt_2$ (100 mol %), $Et_2AlCl$ (100 mol %), $Sc(OTf)_3$ (5 mol %) or $Yb(OTf)_3$ (5 mol %) was used, respectively.