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A metalation strategy for the construction of functionalized naphthalenes: the first synthesis of guieranone A

Malcolm W. B. McCulloch and Russell A. Barrow*

Department of Chemistry, The Australian National University, Canberra ACT 0200, Australia

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Abstract—The first synthesis of the natural product guieranone A is described, demonstrating a one-pot procedure for the synthesis of protected-1,3,6,8-tetraoxygenated naphthalenes and a subsequent directed metalation synthesis of 2-keto naphthalenes.

Syntheses of 2-acyl substituted naphthalenes are difficult to achieve regioselectively, yet these compounds are key building blocks for a large number of naphthalene-based natural products including naphthopyrones and some naphthoquinones. This diverse class of natural products possesses a range of biological activities and new methods to synthesize them are required.[1] This communication outlines a short and efficient synthesis of guieranone A (**1**)[2] showcasing a directed metalation strategy that we are developing which should provide access to a variety of naphthalene-based natural products and derivatives.

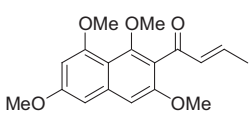
Guieranone A (**1**) is an antifungal agent isolated from the leaves of the plant *Guiera senegalensis* by Silva and Gomes.[2] The position of the butenone moiety in guieranone A—situated on the naphthalene ring *ortho* to two methoxy groups—suggested an *ortho*-directed metalation reaction as an appropriate synthetic strategy. We proposed to utilize both the synthetically useful methoxy directed metalation group (DMG) and the powerful diethyl carbamate[3] DMG in the synthesis of the natural product, and in preparing 2-keto naphthalene analogues.

While the naphthalene synthon required to prepare **1** via this strategy is known, previous syntheses of 1,3,6,8-tetramethoxynaphthalene (**7**) have been inefficient.[4,5] We have developed a high-yielding, one-pot synthesis of protected naphthalenes such as **7** and **8** from the phenylacetic acid derivative **5**.

Our synthesis (Scheme 1) began with methyl 3,5-dimethoxyphenylacetate (**4**), which was readily prepared following Pang's method.[6] This was acylated with acetic anhydride containing a catalytic amount of perchloric acid, in a slight modification of Bycroft's procedure to give **5**.[7]

Treatment of **5** in DMF with 3.3 equiv of sodium hydride gave the naphthalene disodium salt intermediate **6**, via a Dieckmann-type cyclization. The excess of base prevented formation of the phenol **2**,[8] which contains a *peri* six-centered hydrogen bond. These *peri* hydrogen bonds make phenol substitution difficult; for example, Kamila et al. found that the phenol in naphthalene **3** was relatively unreactive towards substitution.[9]

Attempts to synthesize protected 1,3,6,8-tetraoxygenated naphthalenes by quenching the intermediate **6** with soft electrophiles such as iodomethane or MOM-Cl, repeatedly led to the formation of complex mixtures. However, when the relatively hard electrophiles dimethyl sulfate or diethylcarbamoyl chloride were utilized, the naphthalenes **7** and **8** were formed cleanly in 85% and 89% respective yields. Soft electrophiles can



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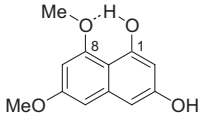

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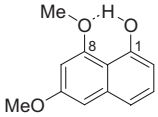

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Keywords: Guieranone; Naphthalenes; Metalation; Natural product; Dieckmann cyclization.
* Corresponding author. Tel.: +61 2 61253419; fax: +61 2 61250760; e-mail: rab@anu.edu.au

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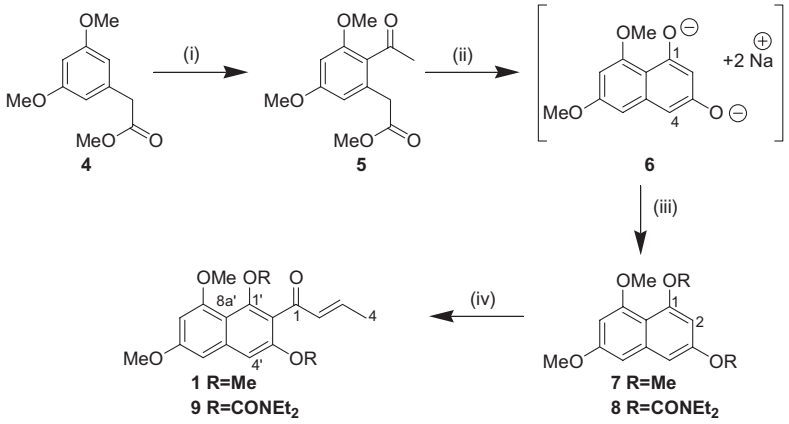

Scheme 1. Reagents, conditions and yields: (i) Ac_2O, $HClO_4$ (cat), 24 h, 85%; (ii) 3.3 equiv NaH, DMF, 2 h; (iii) for **7**, $(CH_3)_2SO_4$, 12–48 h, 85%; for **8**, $ClCONEt_2$, 72 h, rt, then reflux 2 h, 89%; (iv) for **1**, 1.4 equiv *n*-BuLi, 1.4 equiv TMEDA, THF, −78 °C, 1 h, then 70 min, rt, then −78 °C, 1.6 equiv crotonic anhydride to rt, 28% (unoptimized); for **9**, 1.3 equiv *t*-BuLi, 1.3 equiv TMEDA, THF, −78 °C, 45 min, then 40 min, −40 °C, then −78 °C, 2.0 equiv crotonic anhydride to rt, 61% (unoptimized).

presumably react with the soft carbon center in **6**, given that **6** is effectively an enolate.

With naphthalenes **7** and **8** in hand, a final metalation step gave us our desired 2-keto naphthalenes. Thus, when **7** was treated with 1.4 molar equivalents of *n*-BuLi and TMEDA, followed by excess crotonic anhydride,[†] guieranone A (**1**) was obtained in an unoptimized 28% isolated yield (~80% based on recovered starting material). Similarly, when **8** was treated with 1.3 molar equivalents of *t*-BuLi and TMEDA, followed by excess crotonic anhydride, **9** was obtained in 61% isolated yield.[10] While these results are unoptimized, the higher yield of **9** reflects the relative strength of the carbamate DMG.[3]

The spectroscopic data (IR, MS, and NMR) of our synthetic guieranone A sample supported the assigned structure **1**; the data were identical to those reported for the natural product.[2] Table 1 shows that the ^{13}C NMR shifts for synthetic **1** match those of the natural product within the bounds of spectral resolution.

Silva reported that guieranone A showed potent activity against the fungus *C. cucumerinum*.[2] To explore the extent of this antimicrobial activity we have tested **1** against a range of microorganisms using the disk diffusion method[11] at concentrations up to 0.6 mg/mL and found no activity against an unidentified *Penicillium* sp. or against any of the following bacterial pathogens: *S. aureus*, *E. coli*, *P. aeruginosa*, *S. epidermidis*, or *M. smegmatis*. These results indicate that guieranone A possesses selective and specific antifungal activity.

In conclusion, we have completed the first synthesis of guieranone A (**1**) and developed a versatile synthesis of 2-keto naphthalenes. By starting with various phenylacetic acid derivatives, and using a range of different electrophiles in the cyclization/protection and metalation steps, this methodology can give a range of highly functionalized naphthalene derivatives. This will be further elaborated in a forthcoming full paper.

[†] Freshly prepared by DCC dehydration of crotonic acid and then distilled.

Table 1. Comparison of synthetic and natural guieranone (**1**) ^{13}C NMR shifts

Position	Synth. δ_C[a]	Lit.[2,b]
1	197.8	197.9
2	135.2	135.2
3	149.4	149.3
4	18.5	18.4
1′	155.6	155.6
1′-OMe	64.2	64.2
2′	122.7	122.8
3′	156.4	156.5
3′-OMe	56.3	56.3
4′	103.4	103.4
4a′	140.7	140.8
5′	99.8	99.8
6′	160.8	160.9
6′-OMe	56.1	56.1
7′	98.4	98.3
8′	158.6	158.7
8′-OMe	55.8	55.8
8a′	111.5	111.6

[a] 75 MHz APT; CD_3OD.
[b] 100 MHz; CD_3OD.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.127.

References and notes

1. McCulloch, M. W. B.; Barrow, R. A. *Molecules*, in press.
2. Silva, O.; Gomes, E. T. *J. Nat. Prod.* **2003**, *66*, 447–449.
3. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.
4. Eisaku, M.; Shibata, S. *Chem. Pharm. Bull.* **1967**, *15*, 1765–1771.
5. Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 231–235.
6. Pang, Y. P.; Kozikowski, A. P. *J. Org. Chem.* **1991**, *56*, 4499–4508.
7. Bycroft, B. W.; Roberts, J. C. *J. Chem. Soc.* **1962**, 2063–2064.
8. Bycroft, B. W.; Roberts, J. C. *J. Chem. Soc.* **1963**, 4868–4872.
9. Kamila, S.; Mukherjee, C.; Mondal, S. S.; De, A. *Tetrahedron* **2003**, *59*, 1339–1348.
10. Satisfactory spectroscopic data were obtained for all compounds. Selected data: Compound **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.62 (2H, d, 2.3 Hz), 6.36 (2H, d, 2.3 Hz), 3.92 (6H, s), 3.88 (6H, s); ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ: 158.6, 158.4, 139.0 (C-4a), 108.5 (C-8a), 98.3 (C-4), 96.5 (C-2), 56.0 (C-1–OCH_3), 55.1 (C-3–OCH_3); EIMS *m*/*z* (%): 248 (100), 205 (9), 175 (12); HREI-MS *m*/*z*: found 248.1049 ($C_{14}H_{16}O_4$ requires 248.1049). Compound **8**: IR (film): 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (1H, d, 2.3 Hz), 6.83 (1H, d, 2.3 Hz), 6.67 (1H, d, 2.2 Hz), 6.41 (1H, d, 2.2 Hz), 3.84 (3H, s), 3.82 (3H, s), 3.55–3.33 (8H, m, $CON(CH_2CH_3)_2$), 1.31–1.19 (12H, m, $CON(CH_2CH_3)_2$); ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ: 158.4 (C-6), 156.6 (C-8), 154.6 ($CONEt_2$), 153.7 ($CONEt_2$), 149.4 (C-3), 148.1 (C-1), 137.5 (C-4a), 115.2 (C-4), 113.5 (C-8a), 113.2 (C-2), 98.5 (C-5), 98.3 (C-7), 55.4 (OCH_3), 55.2 (OCH_3), [42.4, 42.1, 42.0, 41.6 ($CON(CH_2CH_3)_2$)], [14.1, 13.9, 13.4, 13.1 ($CON(CH_2CH_3)_2$)]. EIMS *m*/*z* (%): 418 (53), 100 (100), 72 (55); HREI-MS *m*/*z*: found 418.2096 ($C_{22}H_{30}N_2O_6$ requires 418.2104). Compound **9**: IR (film): 1720, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (1H, s), 7.13 (1H, dq, 15.6, 6.9 Hz), 6.66 (1H, d, 2.0 Hz), 6.39 (1H, d, 2.0 Hz), 6.03 (1H, dq, 15.6, 1.8 Hz), 3.81 (3H, s), 3.72 (3H, s), 3.42–3.15 (8H, m), 1.92 (3H, dd, 6.9, 1.8 Hz), 1.18–0.97 (12H, m); ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ: 164.1 (C-1), 163.9 ($CONEt_2$), 158.8 (C-6′), 156.6 (C-8′), 152.9 ($CONEt_2$), 146.2 (C-3), 145.5, 143.5, 136.9 (C4a′), 121.8 (C-2), 120.7 (C-2′), 116.7 (C-4′), 112.6 (C-8a′), 99.1 (C-7′), 98.7 (C-5′), 55.8 (6′-OCH_3), 55.2 (8′-OCH_3), [42.7, 42.1, 41.9, 38.1 ($CON(CH_2CH_3)_2$)], 18.0 (C-4), [14.0, 13.4, 13.2, 12.6 ($CON(CH_2CH_3)_2$)]; EIMS *m*/*z* (%): 486 (28), 418 (34), 403 (20), 346 (27), 100 (100), 72 (54); HREI-MS *m*/*z*: found 486.2366 ($C_{26}H_{34}N_2O_7$ requires 486.2366). Compound **1**: ^{1}H NMR (300 MHz, CD_3OD) δ: 7.01 (1H, s), 6.81 (1H, d, 2.0 Hz), 6.61 (1H, dq, 15.5, 6.7 Hz), 6.47 (1H, d, 2.0 Hz), 6.35 (1H, dq, 15.5,1.6 Hz), 3.91 (3H, s), 3.88 (3H, s), 3.83 (3H, s), 3.71 (3H, s), 1.90 (3H, dq, 6.7, 1.6 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.83 (1H, s), 6.66 (1H, d, 2.0 Hz), 6.58 (1H, dq, 15.5, 6.5 Hz), 6.40 (1H, d, 2.0 Hz), 6.38 (1H, dq, 15.5, 1.5 Hz), 3.93 (3H, s), 3.88 (3H, s), 3.82 (3H, s), 3.76 (3H, s), 1.86 (3H, dd, 6.5, 1.5 Hz); ^{13}C APT-NMR (75 MHz, CD_3OD) see Table 1; ^{13}C APT-NMR (75 MHz, $CDCl_3$) δ: 195.5 (C-1′), 159.0 (C-6′), 157.4 (C-8′), 155.2 (C-3′), 154.5 (C-1′), 147.0 (C-3), 138.8 (C-4a′), 134.2 (C-2), 122.0 (C-2′), 110.6 (C-8a′), 101.9 (C-4′), 98.3 (C-5′), 97.0 (C-7′), 63.9 (C-1′-OCH_3), 55.8 (C-8′-OCH_3), 55.5 (C-3′-OCH_3), 55.2 (C-6′-OCH_3), 18.3 (C-4); HREI-MS *m*/*z*: found 316.1310 ($C_{18}H_{20}O_5$ requires 316.1311).
11. National Committee for Clinical Laboratory Standards (NCCLS). *Performance Standards for Antimicrobial Disk Susceptibility Tests*; Approved standard. 7th edn., M2-A7. NCCLS, Wayne, PA, 2000.