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A Diels–Alder strategy towards a benzonaphthopyranoquinone

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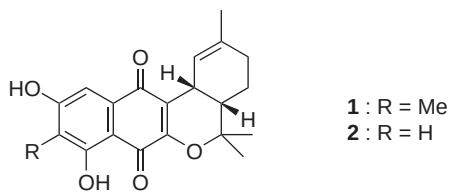
Abstract—Reaction of a suitably protected aryllithium derivative with citral, and subsequent deprotection and cyclization was used to obtain dibenzopyran **5**, a precursor of the tricyclic quinone **6**. Diels–Alder reaction of **6** with 1,3-dimethoxy-1-trimethylsilyloxy-1,3-butadiene **7** led to benzonaphthopyranoquinone **8**. The regioselectivity in the dienophilic partner is governed by the remote oxygen of the pyran ring.

Naphtho[2,3-*b*]pyranoquinones constitute an important class of compounds due to their interesting biological activities.[1] Naphterpin (**1**) and naphthgeranine A (**2**), a new type of benzonaphthopyranoquinone, have been isolated from *Streptomyces* sp[2–4] (Scheme 1). The structural elucidation of these compounds was based on their spectroscopic properties, but no synthetic attempts were reported.

Following our studies on the synthesis of heterocyclic quinones with potential biological activity,[5] we were interested in the preparation of compounds **1** and **2**. Recently, we described the synthesis of the carbon framework of naphthgeranine A in one step, using a tandem-Knoevenagel hetero-Diels–Alder reaction, although in low yield.[6]

A useful approach to naphtho[2,3-*b*]pyranoquinones is the Diels–Alder reaction of benzopyranoquinones with dienes,[7] that has the possibility for variation of the substitution patterns on the aromatic nucleus. In this communication we report the synthesis of the racemic dimethylether derivative of naphthgeranine A using a Diels–Alder methodology (Scheme 2).



1 : R = Me
2 : R = H

Scheme 1.

An interesting method to obtain 2,2-dialkyl-2*H*-1-benzopyrans is the reaction of suitably protected aryllithium derivatives with α,β-unsaturated aldehydes, followed by subsequent deprotection and cyclization.[8] However, this route has not yet been used to obtain the dibenzopyran **5** precursor of the tricyclic quinone **6**. In this aim, phenol **3**,[9] protected as its methoxymethyl ether, was treated with *n*-BuLi in THF at −78°C followed by addition of citral to give alcohol **4** in 78% yield. Hydrolysis of the protecting group of **4** with 6N HCl in THF and subsequent cyclization induced by the acidic medium gave the tricyclic compound **5** (40%). The coupling constant between H-6a and H-10a ($J = 5.1$ Hz) determined by spin decoupling experiments indicates a *cis* stereochemistry for **5** in agreement with the *cis*-Δ^9-tetrahydrocannabinol system.[10] The oxidative demethylation of **5** with silver (II) oxide and nitric acid gave the tricyclic quinone **6** (75%).[11] Finally the Diels–Alder reaction of **6** with diene **7**[12] afforded benzo[*b*]naphtho[2,3-*b*]pyran-7,12-dione **8** in 70% yield.[13]

Molecular orbital calculations of HOMO and LUMO coefficients for diene **7** and quinone **6** were performed by the semiempirical method PM3[14] using Spartan.[15] In the HOMO of diene **7**, the coefficient on C-4 (0.561) is larger than on C-1 (0.383) while in the LUMO of quinone **6** the coefficients are 0.497 and 0.405 for C-2

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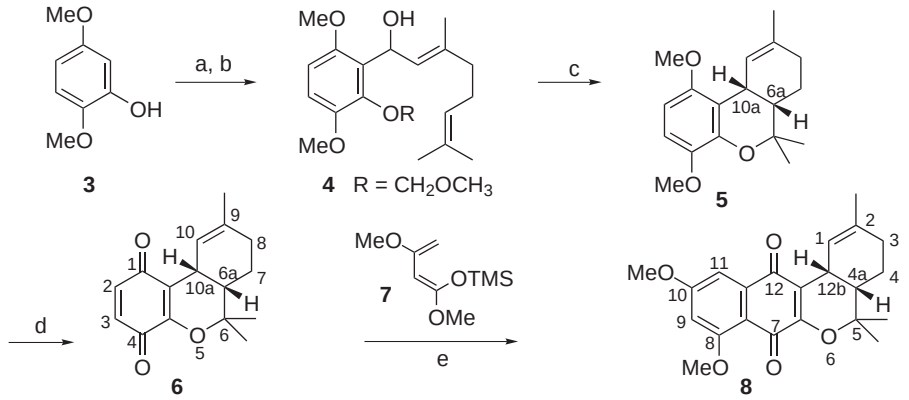

Scheme 2. Reagents: (a) NaH/THF −30°C, $ClCH_2OCH_3$, 95%; (b) *n*-BuLi/THF −78°C, citral, 78%; (c) 6N HCl/THF, 45°C, 40%; (d) AgO/THF, 6N HNO_3, 75%; (e) CH_2Cl_2, SiO_2, 70%.

and C-3, respectively. Thus, FMO theory suggests for quinone **8** the regiochemistry shown in Scheme 2.

The structural assignment for compound **8** is established from its spectral data. First, the ^1H NMR spectrum of **8** shows signals for three methyl groups at δ 1.32, 1.54 and 1.69 ppm, an allylic proton at δ 3.49 ppm and a vinylic proton at δ 6.05 ppm. These signals are similar to those of the natural product **2**.[3] Then, ^1H-^{13}C HMQC and HMBC correlations performed at 500 and 125 MHz allow to assign all protons and carbons except the two gem CH_3-5 and the two OCH_3 at C-8 and C-10. Finally, the use of HMBC results in combination with ^{13}C NMR data confirms the orientation of the Diels–Alder reaction. As it is known for analogous products, the carbonyl adjacent to the pyran oxygen is shifted to high field.[2–4,16] On this basis, the signals at 178.0 and 184.8 ppm are assigned to CO-7 and CO-12, respectively. Then, the presence of a strong ^3J HMBC correlation between H-11 and C-12 enabled H-11 to be assigned thus providing the regiochemistry for compound **8**.

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References

1. (a) Berdy, J. *Handbook of Antibiotic Compounds*; CRC Press: Florida, 1980; Vol. III, pp. 221–279; (b) Hayashi, T.; Smith, F. T.; Lee, K.-H. *J. Med. Chem.* **1987**, *30*, 2005–2008; (c) Itokawa, H.; Matsumoto, K.; Morita, H.; Takeka, K. *Phytochemistry* **1992**, *31*, 1061–1062; (d) Sendl, A.; Chen, J. L.; Jolad, S. D.; Stoddart, C.; Rozhon, E.; Kernan, M.; Nanakorn, W.; Balick, M. *J. Nat. Prod.* **1996**, *59*, 808–811.
2. Shin-Ya, K.; Imai, S.; Furihata, K.; Hayakawa, Y.; Kato, Y.; Vanduyne, G. D.; Clardy, J.; Seto, H. *J. Antibiot.* **1990**, *43*, 444–447.
3. Wessels, P.; Göhrt, A.; Zeeck, A.; Drautz, H.; Zähner, H. *J. Antibiot.* **1991**, *44*, 1013–1018.
4. Shin-Ya, K.; Shimazu, A.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1992**, *45*, 124–125.
5. (a) Tapia, R. A.; Gárate, M. C.; Valderrama, J. A.; Jenkins, P. R.; Fawcett, J.; Russell, D. R. *Tetrahedron Lett.* **1997**, *38*, 153–154; (b) Tapia, R. A.; Gárate, M. C.; Valderrama, J. A.; Jenkins, P. R. *Heterocycles* **1998**, *48*, 1365–1371; (c) Tapia, R. A.; Centella, C. R.; Valderrama, J. A. *Synth. Commun.* **1999**, *29*, 2163–2168.
6. Tapia, R. A.; Navarro, O.; Alegría, L.; Valderrama, J. A. *Heterocycl. Commun.* **1998**, *4*, 151–154.
7. (a) Tapia, R. A.; Valderrama, J. A.; Quintanar, C. *Heterocycles* **1994**, *38*, 1797–1804; (b) Zuloaga, F.; Tapia, R. A.; Quintanar, C. *J. Chem Soc. Perkin Trans.* 2 **1995**, 939–943.
8. Cruz-Almanza, R.; Pérez-Flores, F.; Lemini, C. *Heterocycles* **1994**, *37*, 759–774.
9. Wriede, V.; Fernandez, M.; West, K. F.; Harcourt, D.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 4485–4489.
10. Uliss, D. B.; Razdan, R. K.; Dalzell, H. C.; Handrick, G. R. *Tetrahedron* **1977**, *33*, 2055–2059.
11. Mp 122–123.5°C; IR 1675 and 1640 (C=O) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.30 (s, 3 H, CH_3-6), 1.52 (s, 3 H, CH_3-6), 1.67 (s, 3 H, CH_3-9), 1.2–2.1 (m, 5H, H-6a, CH_2-7, CH_2-8), 3.37 (br t, 1 H, H-10a), 5.98 (m, 1 H, H-10), 6.57 (d, 1 H, J=10.5 Hz, H-2 or H-3), 6.62 (d, 1 H, J=10.5 Hz, H-3 or H-2). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 20.3 (C-7), 23.5 ($\underline{C}H_3$-9), 24.9 ($\underline{C}H_3$-6), 25.7 ($\underline{C}H_3$-6), 29.7 (C-8), 30.6 (C-6a), 39.7 (C-10a), 80.3 (C-6), 120.1 (C-10), 121.3 (C-4a), 133.3 (C-2 or C-3), 136.0 (C-9), 137.8 (C-3 or C-2), 150.9 (C-10b), 182.1 (C-4), 187.3 (C-1); Anal calcd for $C_{16}H_{18}O_3$: C, 74.40, H, 7.02; found: C, 74.20, H, 6.80.
12. Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455–3464.
13. Mp 227–229°C; IR 1675 and 1645 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3 H, CH_3-5), 1.54 (s, 3 H, CH_3-5), 1.69 (s, 3 H, CH_3-2), 1.74 (m, 1H, H-4a), 1.97 (m, 2H, CH_2-4), 2.0 (m, 2 H, CH_2-3), 3.49 (br t, 1 H, H-12b), 3.91 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 6.05 (d, 1 H, J=5.3 Hz, H-1), 6.60 (d, 1 H, J=2.6 Hz, H-9), 7.20 (d, 1 H, J=2.6 Hz, H-11). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ 20.7 (C-4), 24.0 ($\underline{C}H_3$-2), 25.4 ($\underline{C}H_3$-5), 26.1 ($\underline{C}H_3$-5), 30.2 (C-3), 31.2 (C-12b), 40.2 (C-4a), 56.3 ($O\underline{C}H_3$-8 or $O\underline{C}H_3$-10), 56.8 ($O\underline{C}H_3$-10 or $O\underline{C}H_3$-8), 80.5

(C-5), 103.5 (C-9), 103.6 (C-11), 113.8 (C-7a), 120.9 (C-12a), 121.2 (C-1), 136.0 (C-2), 137.5 (C-11a), 154.1 (C-6a), 162.3 (C-8), 165.2 (C-10), 178.0 (C-7), 184.8 (C-12); HRMS calcd for $C_{22}H_{25}O_5$: 369.17019 (MH^+); found 369,17022.

14. Stewart, J. J. P. *J. Comp. Chem.* **1989**, *10*, 209–221.
15. Spartan, version 5.0.3, Wavefunction Inc., 1998.
16. Pathirana, C.; Jensen, P. R.; Fenical, W. *Tetrahedron Lett.* **1992**, *33*, 7663–7666.