Pergamon

Tetrahedron Letters 40 (1999) 4437–4438

TETRAHEDRON LETTERS

First Total Synthesis of (±)-Brasiliquinone B

Mahesh L. Patil, Hanumant B. Borate, Datta E. Ponde, Baburao M. Bhawal and Vishnu H. Deshpande*

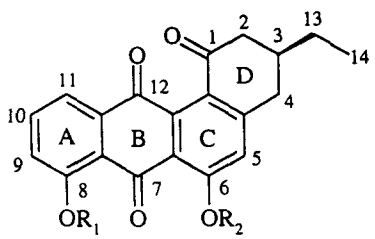
Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune-411 008 ,India

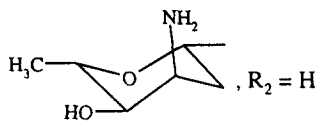
Received 12 March 1999; accepted 19 April 1999

Abstract: Brasiliquinone B (**2**) was synthesized from 7-methoxy-1-tetralone in 8 steps making use of Friedel-Crafts alkylation as a key step.

Keywords: Brasiliquinone B, angucyclines, antibiotics, Friedel-Crafts alkylation.

Brasiliquinones A-C, isolated from pathogenic species of *Nocardia* [1,2], are the novel cytotoxic benz(a)anthraquinones, commonly known as angucyclines. Most of the angucycline antibiotics have a methyl group at C-3 whereas brasiliquinones A-C possess an ethyl group at C-3 constituting a new group of angucyclines. It has been shown that these angucycline antibiotics are active against multiple drug resistant tumor cells. Brasiliquinones B and C are more effective than brasiliquinone A against L1210 tumor cells [1]. There are several reports on the isolation and biological activities of angucycline antibiotics [3] but very few attempts have been made to synthesize these highly potent molecules [4] and there is no report on the synthesis of brasiliquinones A-C. We describe herein the first total synthesis of (±)-brasiliquinone B.



1. Brasiliquinone A : R_1 = 

, R_2 = H

2. Brasiliquinone B : $R_1 = R_2 = H$

3. Brasiliquinone C : R_1 = Me, R_2 = H

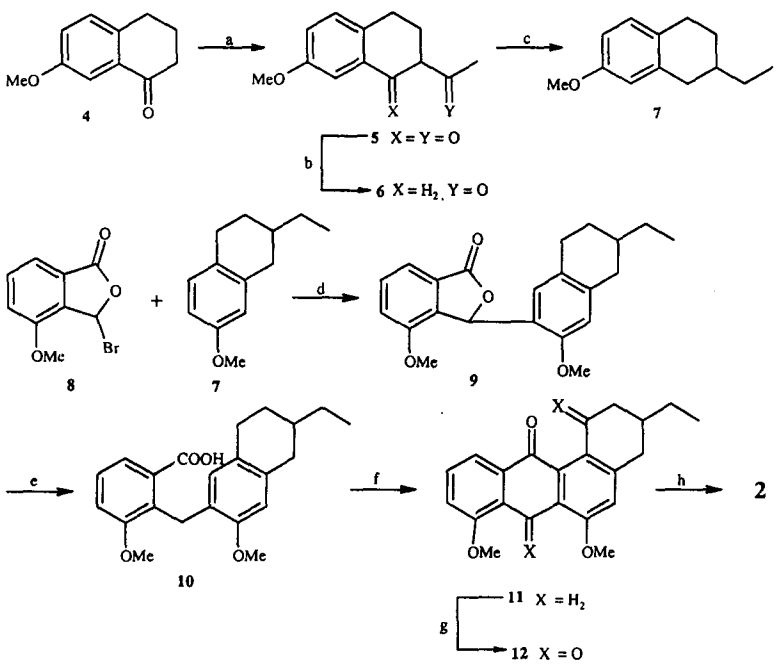
Synthesis of angucycline antibiotics with a hydroxy group at C-6 poses problems as there are reports of spontaneous aromatization or carbon-carbon bond cleavage in reactions using a Diels-Alder approach [5]. We envisioned the use of a Friedel-Crafts alkylation to build up the angucycline skeleton and achieved the synthesis of (±)-brasiliquinone B starting from 7-methoxy-1-tetralone as shown in Scheme-1.

The key intermediate **7**, though simple in structure, is not known in literature. Efforts to alkylate 7-methoxy-1-tetralone with ethyl iodide to obtain the corresponding 2-ethyl tetralone, which could be reduced to afford tetralin **7**, were unsuccessful as the dialkylated product was formed in considerable amounts in most of the conditions used for alkylation. Finally, this problem was solved by acylating the 7-methoxy-1-tetralone with acetic anhydride in presence of boron trifluoride etherate to obtain 2-acetyl-7-methoxy-1-tetralone (**5**) which was hydrogenated followed by Clemmensen reduction to afford the required tetralin derivative **7**.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00766-2

Friedel-Crafts alkylation of **7** with 3-bromo-4-methoxyphthalide (**8**) [6] in presence of stannic chloride afforded regiospecifically the lactone **9** which was reductively opened to provide the acid **10**. Cyclization of **10** with trifluoroacetic anhydride resulted in the formation of anthrone **11** which was oxidized with chromium trioxide in acetic acid to yield the brasiliquinone B dimethyl ether (**12**) in good yield. Reaction of **12** with aluminium trichloride brought about the desired demethylation to afford (±)-brasiliquinone B (**2**) which showed spectroscopic characteristics [7] identical to those in the literature [1].

Scheme-1



a) i) Ac_2O, $BF_3.Et_2O$, RT, 2h. ii) CH_3COONa, MeOH, 4h, reflux, 65%; b) H_2, 10 % Pd/C, HCl, MeOH, 8h, 60%; c) Zn/Hg, HCl, 12h, 77%; d) $SnCl_4$, CH_2Cl_2, 0 °C, 1h, 84%; e) Zn, Pyridine, $CuSO_4.5H_2O$, 1N NaOH, reflux, 10h., 85%; f) TFAA, CH_2Cl_2, 0 °C, overnight, 64%; g) CrO_3, AcOH, 0°C to RT, overnight 93%; h) $AlCl_3$, 0°C, 10h., 80%.

Acknowledgements: MLP and DEP thank CSIR, New Delhi for the award of senior research fellowship.

References and Notes:

1) Tsuda, M., Sato, H., Tanaka, Y., Yazawa, K., Mikami, Y., Sasaki, T. and Kobayashi, J. *J. Chem. Soc., Perkin Trans.1* **1996**, 1773.

2) a) Nemoto, A., Tanaka, Y., Karasaki, Y., Komaki, H., Yazawa, K., Mikami, Y., Tojo, T., Kadowaki, K., Tsuda, M. and Kobayashi, J. *J. Antibiotics* **1997**, *50*, 18; b) For correction see, *J. Antibiotics*, **1997**, 50 (4), C-1.

3) Rohr, J. and Thiericke, R., *Nat., Prod., Rep.* **1992**, *9*, 103.

4) Krohn, K. and Rohr, J. *Top. Curr. Chem.* **1997**, *118*, 127.

5) a) Guingant, A. and Barreto, M. *Tetrahedron Lett.* **1987**, *28*, 3107. b) Larsen, D. and O'Shea, M. *J. Chem. Soc., Perkin Trans.1* **1995**,1019.

6) Kim, K., Vanotti, E., Suarato, A. and Johnson, F. *J. Am. Chem. Soc.* **1979**, *101*, 2483.

7) All new compounds gave satisfactory spectroscopic data: (±)-Brasiliquinone B, (**2**), m.p.187-191°C, Literature [1] m.p.187-190°C; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.00 (t, J=7Hz, 3H), 1.40-1.80 (m, 2H), 2.00-2.20 (m, 1H), 2.35-2.70 (m, 2H), 2.90-3.08 (m, 2H), 7.02 (s, 1H), 7.22-7.32 (m, 1H), 7.60-7.75 (m, 2H), 11.70 (s, 1H), 12.30 (s, 1H); MS: m/z 336 (M^+), 308.