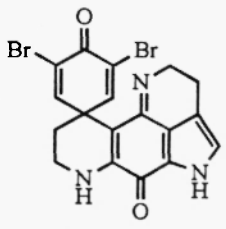
SYNTHESIS OF A FURANO[4,3,2-*de*]QUINOLINE NUCLEUS: A DERIVATIVE OF THE DISCORHABDIN ALKALOIDS

Qizhu Ding, Rulin Zhao and J. William Lown*

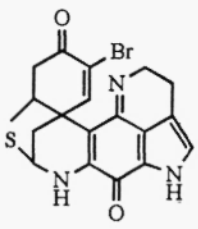
Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2

Abstract: A novel method of synthesis of furanoquinoline nucleus structurally related to discorhabdin alkaloids from pyrogallol is developed. Proof of the position of the key nitration step was obtained by x-ray diffraction analysis of an intermediate **4**.

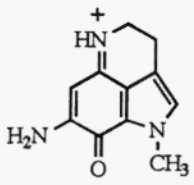
Discorhabdin C was isolated from the sponge of *Latrunculia* du Bocage in New Zealand, which exhibits extreme toxicity toward tumor cells (p338 and L1210) (1). Recently, some physiologically active substances, such as prianosins (2), makaluvamines (3) and isobatzellines (4), were isolated from marine sources. All of these compounds have the same unique highly-fused structure as discorhabdin C, *i.e.* the pyrrolo[4,3,2-*de*]quinoline skeleton. The novel structures and physiological properties of these natural products have prompted many groups to initiate their syntheses (5). Interest in these tricyclic systems is therefore increasing and some derivatives of pyrroloquinolines have been synthesized and their antitumor properties are studied (6).



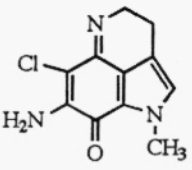
Discorhabdin C



Prianosin A



Makaluvamine A



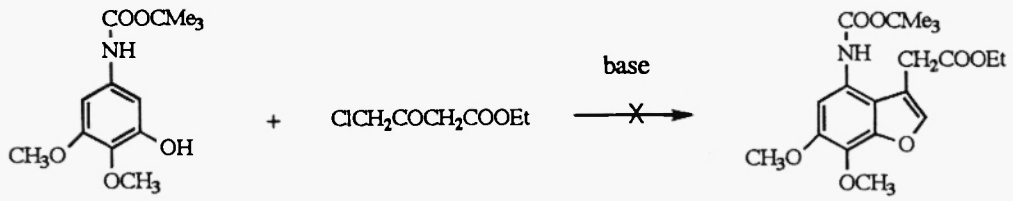
Isobatzelline C

Bakare (7) and co-workers have described the synthesis of the 2-azo analog of pyrrolo[4,3,2-*de*]quinoline for further elaboration into potential drugs which would have the pyrazolo[5,4,3-*de*]quinoline skeleton.

Furano[4,3,2-*de*]quinoline nucleus has a similar skeleton as pyrrolo[4,3,2-*de*]quinoline, but this tricyclic system and its derivatives have never been synthesized. We describe herein an efficient synthesis of the furano[4,3,2-*de*]quinoline nucleus.

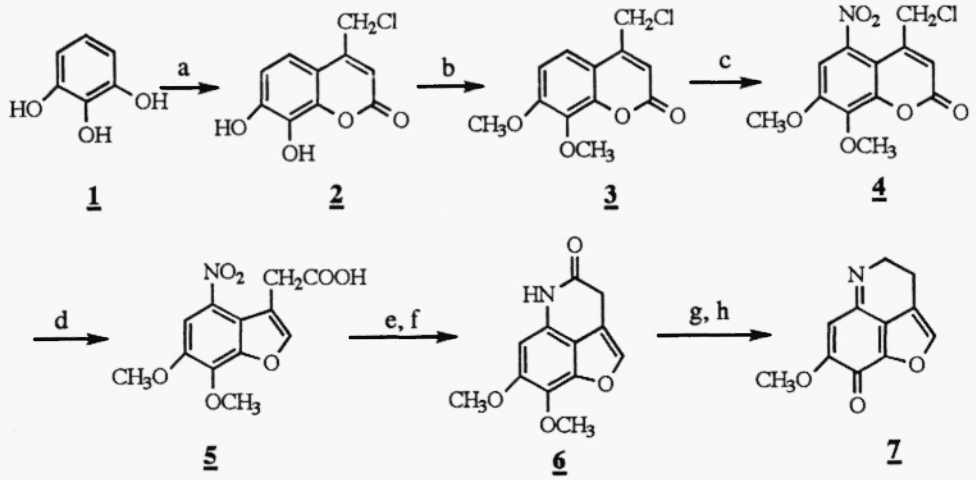
Initially we have attempted to use *N*-(*t*-butoxycarbonyl)-3-hydroxy-4,5-dimethoxyaniline as the starting material to build up the furan ring system with ethyl 4-chloroacetoacetate (scheme I), but this approach proved

unsatisfactory as shown in scheme I. Finally we developed a convenient method to synthesize the furano[4,3,2-*de*]quinoline from pyrogallol as shown in scheme II.



Scheme I

This methodology involves the formation of 4-chloromethyl-7,8-dihydroxycoumarin **2** by the reaction of pyrogallol **1** with ethyl 4-chloroacetoacetate in concentrated sulfuric acid (75% yield). Coumarin **2** was then methylated by Me_2SO_4 to produce 4-chloromethyl-7,8-dimethoxycoumarin **3** (63% yield). Nitration of



Scheme II: (a) $ClCH_2COCH_2COOEt$, H_2SO_4; (b) Me_2SO_4, K_2CO_3; (c) HNO_3; (d) KOH; (e) H_2/Pd/C; (f) EDCI; (g) BH_3•SMe_2; (h) CAN.

coumarin **3** produces a 4-chloromethyl-7,8-dimethoxy-nitrocoumarin (65% yield). In order to identify the position of the nitro group, we have carried out an x-ray crystallographic determination. The results of crystallography (see figure 1, table 1 and 2) show that this nitrocoumarin is 4-chloromethyl-7,8-dimethoxy-5-nitrocoumarin **4** (8). This coumarin was converted to the benzofuran structure **5** (9) (53% yield) by an alkali-mediated rearrangement reaction *via* α,β-unsaturated acid **8** (10) (scheme III). Thus hydrogenation of 3-carboxymethyl-4-nitro-6,7-dimethoxybenzofuran **5** over palladium on charcoal in THF followed by cyclization with EDCI gave the lactam **6** (11) (61%). Finally, the lactam **6** was reduced by BH_3•SMe_2, then oxidized by CAN to produce the furano[4,3,2-*de*]quinoline nucleus **7** (12) as a yellow crystalline product (35% yield).

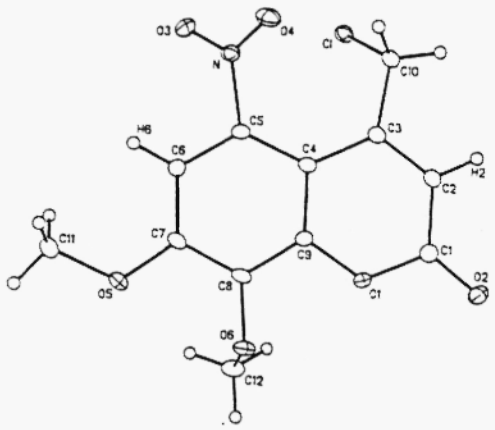


Figure 1. X-ray crystal structure (13) of 4-chloromethyl-7,8-dimethoxy-5-nitrocoumarin **4**

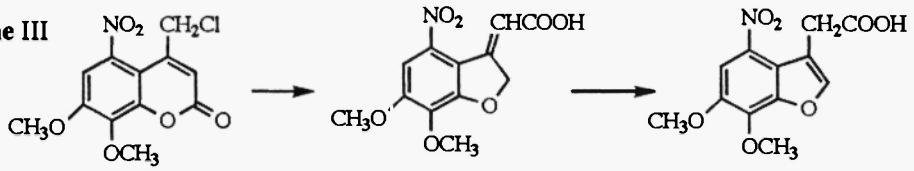
Table 1. Selected interatomic distances (Å) of 4-chloromethyl-7,8-dimethoxy-5-nitrocoumarin **4**

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
Cl	C10	1.795(2)	C1	C2	1.443(3)
O1	C1	1.379(3)	C2	C3	1.345(3)
O1	C9	1.368(3)	C3	C4	1.474(3)
O2	C1	1.200(3)	C3	C10	1.504(3)
O3	N	1.226(3)	C4	C5	1.401(3)
O4	N	1.221(3)	C4	C9	1.412(3)
O5	C7	1.352(3)	C5	C6	1.384(3)
O5	C11	1.429(3)	C6	C7	1.393(3)
O6	C8	1.371(3)	C7	C8	1.384(3)
O6	C12	1.435(3)	C8	C9	1.393(3)
N	C5	1.478(3)			

Table 2. Selected interatomic angles (deg) of 4-chloromethyl-7,8-dimethoxy-5-nitrocoumarin **4**

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C1	O1	C9	122.0(2)	C5	C4	C9	113.6(2)
C7	O5	C11	118.5(2)	N	C5	C4	123.1(2)
C8	O6	C12	113.3(2)	N	C5	C6	112.7(2)
O3	N	O4	124.6(2)	C4	C5	C6	124.1(2)
O3	N	C5	117.1(2)	C5	C6	C7	119.9(2)
O4	N	C5	118.2(2)	O5	C7	C6	125.0(2)
O1	C1	O2	116.9(2)	O5	C7	C8	116.1(2)
O1	C1	C2	115.9(2)	C6	C7	C8	118.8(2)
O2	C1	C2	127.1(2)	O6	C8	C7	121.1(2)
C1	C2	C3	123.9(2)	O6	C8	C9	119.1(2)
C2	C3	C4	118.7(2)	C7	C8	C9	119.8(2)
C2	C3	C10	116.0(2)	O1	C9	C4	122.6(2)
C4	C3	C10	125.3(2)	O1	C9	C8	113.7(2)
C3	C4	C5	130.2(2)	C4	C9	C8	123.8(2)
C3	C4	C9	115.9(2)	Cl	C10	C3	110.9(2)

Scheme III



4 8 5

Details of the antitumor properties of 7 and its lexitropsin conjugates will be reported in due course.

Acknowledgments. We would like to thank the National Cancer Institute of Canada for financial support of this research (to JWL).

References and Footnotes

1. N. B. Perry, J. W. Blunt, M. H. G. Munro, *Tetrahedron*, 44, 1727-1734, (1988).
2. (a) J. Kobayashi, J. Cheng, M. Ishibashi, H. Nakamura, Y. Ohizumi, Y. Hirata, T. Sasaki, H. Lu, J. Clardy, *Tetrahydron Lett.*, 28, 4939-4942, (1987). (b) J. Cheng, Y. Ohizumi, M. R. Wachli, H. Nakamura, Y. Hirata, T. Sasaki, Kobayashi, J. *J. Org. Chem.*, 53, 4621-4624, (1988). (c) J. Kobayashi, J. Cheng, S. Yamamura, M. Ishibashi, *Tetrahydron Lett.*, 32, 1227-1228, (1991).
3. (a) D. C. Radisky, E. S. Radisky, L. R. Barrows, B. R. Copp, R. A. Kramer, C. M. Ireland, *J. Am. Chem. Soc.*, 115, 1632-1638, (1993). (b) L. R. Barrows, D. C. Radisky, B. R. Copp, D. S. Swaffar, R. A. Kramer, R. L. Warters, C. M. Ireland, *Anti-Cancer Drug Design*, 8, 333-347, (1993).
4. H. H. Sun, S. Sekemi, N. Burries, P. McCarthy, *J. Org. Chem.*, 55, 4964-4966, (1990).
5. (a) J. D. White, K. M. Yager, T. Yakura, *J. Am. Chem. Soc.*, 116, 1831-1838, (1994). (b) E. V. Sadanandan, S. K. Pilai, M. V. Lakshmikantham, A. D. Billimoria, J. S. Culpepper, M. P. Cava, *J. Org. Chem.*, 60, 1800-1805, (1995). (c) P. Balczewski, J. A. Joule, C. Estevez, M. Alvarez, *J. Org. Chem.*, 59, 4571-4575, (1994). (d) T. Izawa, S. Nishiyama, S. Yamamura, *Tetrahedron*, 50, 13593-13600, (1994).
6. (a) R. Zhao, B. Oreski, J. W. Lown, *Bioorg. Med. Chem. Lett.*, 6, 2169-2172, (1996). (b) R. Zhao, J. W. Lown, *Synth. Commun.*, 27, 2103-2110, (1997).
7. O. Bakare, L. H. Zalkow, M. Edward, ; E. M. Burgess, *Synth. Commun.*, 27, 1569-1576, (1997).
8. Compound 4: ^{1}H NMR ($CDCl_3$): δ 4.00 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.60 (d, J = 1.2 Hz, 2 H, CH_2), 6.64 (t, J = 1.2 Hz, 1 H, coumarin-H), 7.22 (s, 1 H, Ar-H).
9. Compound 5: Calcd for $C_{12}H_{11}NO_7$ 281.0536, found 281.0531 (M^+, 100%); ^{1}H NMR ($CDCl_3$): δ 3.95 (s, 3 H, OCH_3), 4.00 (d, J = 1.0 Hz, 2 H, CH_2), 4.30 (s, 3 H, OCH_3), 7.65 (t, J = 1.0 Hz, 1 H, furan-H), 7.80 (s, 1 H, Ar-H).
10. Compound 8: Calcd for $C_{12}H_{11}NO_7$ 281.0536, found 281.0532 (M^+, 100%); ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 5.25 (d, J = 2.7 Hz, 2 H, CH_2), 5.95 (t, J = 2.7 Hz, 1 H, CH), 7.20 (s, 1 H, Ar-H).
11. Compound 6: Calcd for $C_{12}H_{11}NO_4$ 233.0687, found 233.0687 (M^+, 100%); ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3 H, OCH_3), 3.95 (d, J = 1.8 Hz, 2 H, CH_2), 4.15 (s, 3 H, OCH_3), 6.30 (s, 1 H, Ar-H), 7.27 (t, J = 1.8 Hz, 1 H, furan-H), 7.85 (s, 1 H, NH).
12. Compound 7: Calcd for $C_{11}H_9NO_3$ 203.0582, found 203.0581 (M^+, 100%); ^{1}H NMR ($CDCl_3$): δ 2.98 (dt, J = 1.2 Hz, 7.2 Hz, 2 H, C-CH_2), 3.85 (s, 3 H, OCH_3), 3.90 (t, J = 7.2 Hz, 2 H, N-CH_2), 5.83 (s, 1 H, Ar-H), 7.65 (t, J = 1.2 Hz, 1 H, furan-H).
13. The crystal structure was solved using the program SHELXL93: Sheldrick, G. M. SHELXL93, University of Göttingen, 1993.

Received on September 4, 1997