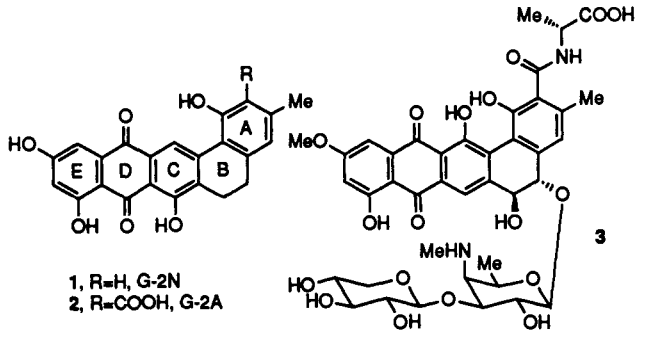
Syntheses of the Benzo[a]naphthacenequinone Pigments G-2N and G-2A

T. Ross Kelly,* Wei Xu, Zhenkun Ma, Qun Li, and Vidya Bhushan

E. F. Merkert Chemistry Center
Department of Chemistry, Boston College
Chestnut Hill, Massachusetts 02167

Received February 25, 1993

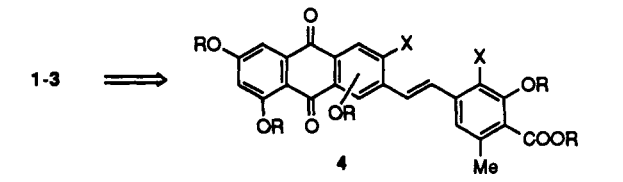
First reported in 1984,[1] G-2N (**1**) and G-2A (**2**) are the archetypal members of a small but growing family[2] of natural products, all of which possess as a common structural feature the pentacyclic benzo[*a*]naphthacenequinone nucleus. Members of this family exhibit a variety of biological activities; perhaps most noteworthy are the anti-HIV[3] and antifungal properties[4] of the more recently characterized—and structurally more complex—siblings typified by pradimicin A (**3**).[2c,d] To date, no



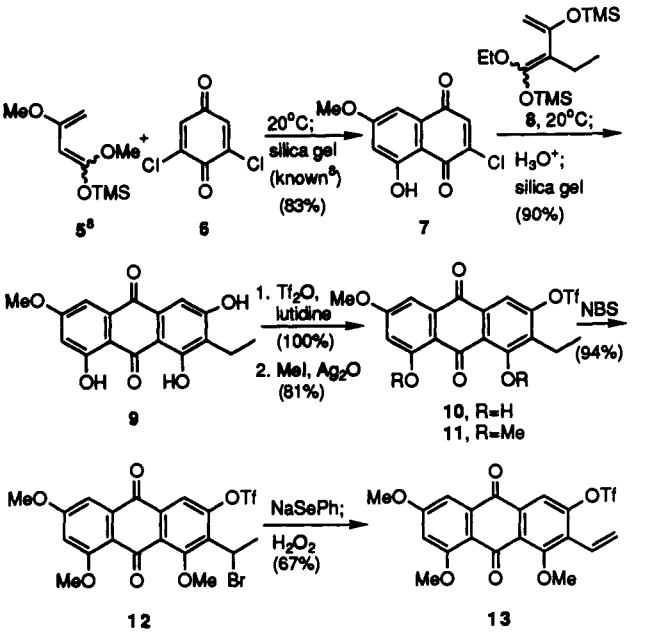
naturally occurring benzo[*a*]naphthacenequinone has been synthesized. We now report the syntheses of G-2N and G-2A. The syntheses employ a regiospecific and potentially general route that we expect can be extended in due course to the preparation of the remaining members of this family.

Retrosynthetic analysis (Scheme I) reinforced by considerations of synthetic economy suggested that **1**–**3**, as well as their congeners, should be available by a unified strategy wherein a stilbene such as **4** plays a key role. Reduction of the stilbene double bond of **4** and then an intramolecular biaryl coupling[5,6] between the two X-bearing carbons leads to the skeleton of G-2N and G-2A,

Scheme I



Scheme II



whereas Sharpless-type[7] asymmetric dihydroxylation of **4** followed by cyclization generates[5] the chiral pentacyclic unit of **3**.

The tricyclic anthraquinone subunit of **4** corresponding to G-2N and G-2A was constructed as shown in Scheme II. Two successive, regiospecific Diels–Alder reactions, whose regiochemical outcomes follow from the work of Brassard,[8] led to the quick assembly of the basic skeleton (we note that despite its apparent complexity, diene **8** can be prepared in a single step from commercially available ethyl α-ethylacetoacetate by reaction with LiN(*i*-Pr)$_2$/TMS-Cl[9]). The non-hydrogen-bonded hydroxyl in **9** was selectively[10] converted to its triflate, the remaining hydroxyls were methylated, and the ethyl side chain was modified to a vinyl group by benzylic bromination, conversion to the selenide,[11] and selenoxide elimination. The overall yield of **13** from **6** is 38%.

Fabrication (Scheme III) of the A-ring synthon **20** commenced with fusion[12] of catechol with dichlorodiphenylmethane to generate ketal **14**,[12] which was ortho-metalated[13] and quenched with *tert*-butyl isocyanate[14] to give **15**. The newly installed amide group in **15** not only can serve as a progenitor of the carboxylic acid/amide units of **2** and **3** but also functions as a directing group for a second ortho metalation. In that instance, a competing metalation of one of the phenyl rings of the benzophenone ketal unit intruded. The simplest rejoinder was to allow the two

(1) For a report of the isolation of G-2N and G-2A and initial (incorrect) structure assignments, see: (a) Gerber, N. N.; Lechevalier, M. P. *Can. J. Chem.* **1984**, *62*, 2818. For revised structure assignments (as **1** and **2**), see: (b) Rickards, R. W. *J. Antibiot.* **1989**, *42*, 336. (c) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555. The latter paper describes a synthesis of the trimethyl ether of the original (incorrect) structure attributed to G-2N.

(2) For more recently identified members see, *inter alia*: (a) KS-619-1, Matsuda, Y.; Kase, H. *J. Antibiot.* **1987**, *40*, 1104. Yasuzawa, T.; Yoshida, M.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 1111. (b) SF2446A1 and analogs, Takeda, U.; Okada, T.; Takagi, M.; Gomi, S.; Itoh, J.; Sezaki, M.; Ito, M.; Miyadoh, S.; Shomura, T. *J. Antibiot.* **1988**, *41*, 417. Gomi, S.; Sasaki, T.; Itoh, J.; Sezaki, M. *J. Antibiot.* **1988**, *41*, 425. (c) Benanomycins, Gomi, S.; Sezaki, M.; Kondo, S.; Hara, T.; Naganawa, H.; Takeuchi, T. *J. Antibiot.* **1988**, *41*, 1019. (d) Pradimicins, Tsunakawa, M.; Nishio, M.; Ohkuma, H.; Tsuno, T.; Konishi, M.; Naito, T.; Oki, T.; Kawaguchi, H. *J. Org. Chem.* **1989**, *54*, 2532. Sawada, Y.; Tsuno, T.; Yamamoto, H.; Nishio, M.; Konishi, M.; Oki, T. *J. Antibiot.* **1990**, *43*, 1367. (e) See also: benastatin A and B, Aoyagi, T.; Aoyama, T.; Kojima, F.; Matsuda, N.; Maruyama, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1992**, *45*, 1385.

(3) Tanabe, A.; Nakashima, H.; Yoshida, O.; Yamamoto, N.; Tenmyo, O.; Oki, T. *J. Antibiot.* **1988**, *41*, 1708. Hoshino, H.; Seki, J. I.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 344.

(4) Saksena, A. K.; Girijavallabhan, V. M.; Cooper, A. B.; Loebenberg, D. *Annu. Rep. Med. Chem.*, Allen, R. C., Ed. **1989**, *24*, 116 and references therein.

(5) For a model study, see: Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161.

(6) For a recent review of biaryl coupling reactions, see: Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. See also: Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 481.

(7) For a leading reference, see: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(8) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455.

(9) Compare: Kelly, T. R.; Behforouz, M.; Echavarren, A.; Vaya, J. *Tetrahedron Lett.* **1983**, *24*, 2331.

(10) Thomson, R. H. *Naturally Occurring Quinones*, 2nd ed.; Academic Press: New York, 1971; p 43.

(11) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

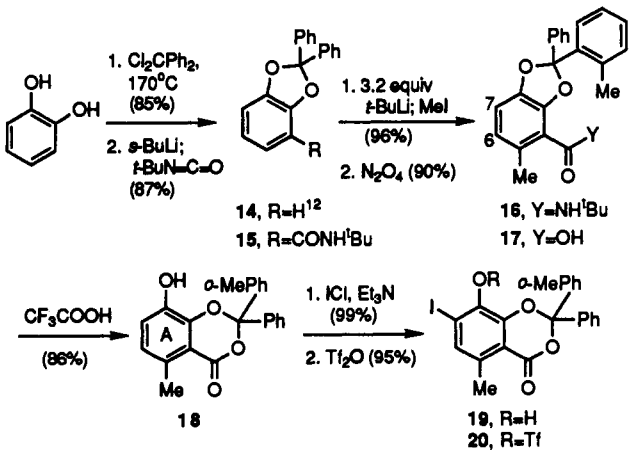
(12) Jurd, L. *J. Am. Chem. Soc.* **1959**, *81*, 4606.

(13) For reviews, see, *inter alia*; Gschwend, H. W.; Rodriguez, H. R. *Org. React. (New York)* **1979**, *26*, 1. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(14) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522 and references therein.

0002-7863/93/1515-5843$04.00/0

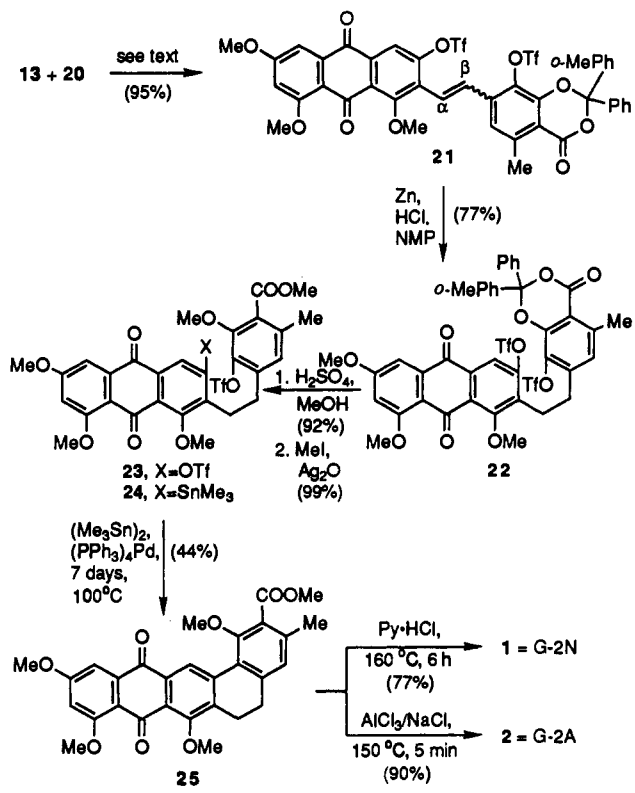
Scheme III



competing reactions to each run their course, generating the doubly methylated species **16** in high yield. The amide group in **16** was then cleaved with N_2O_4 under hydrolytic conditions[14] to afford **17**. Halogenation of **17**, as well as its deprotected dihydroxy analog, proceeded exclusively at the undesired C-6 position under a variety of conditions. Fortunately, however, exposure of **17** to CF_3COOH caused isomerization to **18**, wherein the two A-ring oxygen substituents are substantially differentiated. Now, due to the overriding directing effect of the phenolic hydroxyl, iodination took exclusively the desired regiochemical course, yielding **19**. The phenol moiety, having played its part as a directing group, was then recast as a triflate for a role whose purpose will become apparent shortly. The overall yield of **20** from catechol is 52%.

Given the complexity of the substrates (and the presence of the triflates), it is not surprising that palladium-catalyzed coupling of **13** with **20** proceeded poorly under conventional[15] Heck reaction conditions (Scheme IV). But comprehensive optimization of various unconventional catalyst [$Pd(CF_3CO_2)_2$], ligand [$P(C_6F_5)_3$], base (*i*-Pr_2NH), additive (CF_3CO_2Ag), solvent (THF), and temperature (90 °C, sealed tube) combinations[16] eventually led to **21** in 95% yield. In contrast, however, the seemingly trivial catalytic hydrogenation of the double bond of **21** to give **22** could not be realized under a variety[17] of reaction conditions. That difficulty was overcome in a nonstandard manner by reducing **21** to **22** using zinc and concentrated HCl in *N*-methylpyrrolidinone.[18] Attempts at palladium-catalyzed cyclization of **22** failed. Examination of models of the putative palladacycle intermediate suggested possible destabilizing interactions between the aryl substituents on the C-2 position of the dioxanone ring and ligands on the palladium, so **22** was modified to **23**. Intramolecular biaryl coupling of the two triflate-bearing carbons in **23** to give **25** was then accomplished in one operation through the agency of palladium catalysis in the presence of hexamethylditin.[5,19] The

Scheme IV



course of the reaction was demonstrated by showing that **23** can be converted to **24** in 68% yield and that **24** can be cyclized in 56% yield. Fusion of **25** with pyridine hydrochloride at 160 °C for several hours results in concomitant demethylation[20a] and decarboxylation (a facile reaction of salicylic acids[21]) to give G-2N. Brief exposure of **25** to an $AlCl_3$/NaCl melt[20b] affords G-2A. Synthetic G-2N and G-2A are identical to authentic samples by direct comparison.

The foregoing sequences provide the first syntheses of any members of the benzo[*a*]naphthacenequinone family of natural products. The synthetic routes are regiospecific, convergent, and short. Efforts to extend the general strategy to the synthesis of more complex members of this family are presently underway.

Acknowledgment. Support of this work by a grant from the National Institutes of Health (GM44470) is gratefully acknowledged. We thank Dr. Mary P. Lechevalier[1] for making available authentic samples of G-2N and G-2A, Ms. Jennifer Joy and Ms. Brandy Mauck for assistance in the preparation of starting materials, Dr. Qun Feng for some related studies, Dr. Vittorio Farina for helpful discussions, and Mr. Doug Gage of the NIH-supported regional mass spectroscopy facility at Michigan State University for high-resolution mass spectra.

Supplementary Material Available: Experimental information and spectroscopic data for all compounds described (8 pages). Ordering information is given on any current masthead page.

(15) For reviews, see: Heck, R. F. *Org. React. (New York)* **1982**, *27*, 345. Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelheck, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 833.

(16) Recent papers that contributed to the solution include those of: Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557. Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C., Jr. *J. Org. Chem.* **1990**, *55*, 5833. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859. Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1989**, *54*, 1773. Grigg, R.; Loganathan, V.; Santhakumar, V.; Sridharan, V.; Teasdale, A. *Tetrahedron Lett.* **1991**, *32*, 687.

(17) With H_2 and Pd/C in ethanol, double bond reduction was accompanied by detriflation. Conditions a–f gave complex mixtures: (a) H_2, Raney Ni; (b) H_2, Rh/C; (c) diimide ($TsNHNH_2$, NaOAc); (d) Et_3SiH/CF_3COOH; (e) $NaBH_4/CoCl_2$; (f) $NaBH_4/NiCl_2$. SmI_2 did not reduce the double bond but did reduce off a triflate. Successive treatment with BH_3·THF and CH_3CH_2COOH gave back starting material after exposure to air.

(18) We have not examined the mechanism of this reaction, but the reagents (HCl/Zn) were tried with the hope that the anthraquinone unit would be reduced to the hydroquinone and that successive tautomerizations involving protonations at first the β (see **21**) and then the α carbon would generate **22**. The formation of **22** is consistent with (but does not prove) the involvement of such a mechanism.

(19) For a recent review of Pd-catalyzed reactions of organotin compounds, see: Mitchell, T. N. *Synthesis* **1992**, 803. For intermolecular couplings of anthraquinone triflates, see: Tamayo, N.; Echavarren, A. M.; Paredes, M. C.; Fariña, F.; Noheda, P. *Tetrahedron Lett.* **1990**, *31*, 5189. For other relevant papers, see: Saá, J. M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1992**, *57*, 678. Mori, M.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 3486. Piers, E.; Friesen, R. W.; Keay, B. A. *Tetrahedron* **1991**, *47*, 4555. Stille, J. K.; Su, H.; Hill, D. H.; Schneider, P.; Tanaka, M.; Morrison, D. L.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1993. Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 3859.

(20) (a) Curtis, R. F.; Hassall, C. H.; Parry, D. R. *J. Chem. Soc., Perkin Trans. I* **1972**, 240. Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (b) Cameron, D. W.; Deutscher, D. J.; Feutrill, G. I.; Griffiths, P. G. *Aust. J. Chem.* **1981**, *34*, 2401.

(21) Grimshaw, J. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1976; Vol. IIID, Chapter 15.