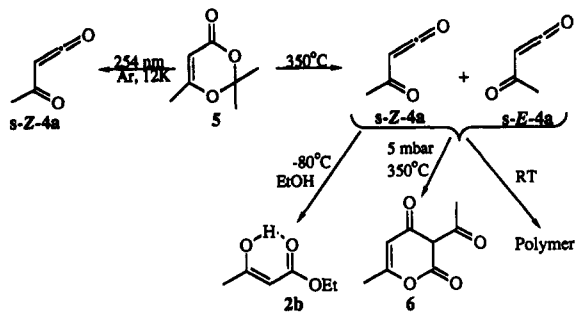
Scheme II



h produced all the ketene bands in the photostationary state. (The carbonyl band of s-*Z*-**4a** produced by photolysis of **5** does not appear at 1687 but at 1675 cm^{-1}, presumably due the vicinity of acetone in the matrix cavity). Photolysis of **5** in 3-methylpentane glass (254 nm, 20 min; 18 K) gave acetone (1718 cm^{-1}) and s-*Z*-**4a** (2143, 1675 cm^{-1}) with no fine structure. Photolysis of **5** in pentane (254 nm; 30 °C) gave the same ketene polymer as obtained on FVP, and photolysis in ethanol solution (254 nm; 30 °C) gave ethyl acetoacetate.[16]

The photoproduct still contains a carbonyl group and a methyl group (1688 and 1385 cm^{-1}, respectively) in an environment very similar to that of the starting material (**4a**) (Figure 1d), and since it also behaves like **4a** chemically and is converted to **4a** on warm up, it is reasonable to conclude that the photoproduct is not a different compound but a set of different conformers, presumably skew, arising from the matrix environment adapting to the excited state structures of the ketenes and thus trapping the ground states in "unnatural" conformations.[17] Such photoconformers were seen also for **4d** (2152, 2112 cm^{-1}) and, weakly, for **4i** (2150 cm^{-1}). **4g,h** showed no photoreaction, probably because the predominant ground-state conformers are already skew s-*E* forms.

The phenomenon reported here is of considerable importance for all matrix–photochemical studies involving ketene-forming reactions. The photochemical Wolff rearrangement is a case in point, where not only multiple bands due to dimethyl ketene have been observed but strong bands that would normally have been ascribed to ketenes have been interpreted as the C=C stretch in dimethyloxirene.[18] While we do not wish to cast doubt on the assignment,[18] and dialkyl ketenes may very well behave differently from acylketenes, our results demonstate a need for a thorough investigation of the photoreactions of ketenes, and we plan such a study.

Acknowledgment. This work was supported by the Australian Research Council and The University of Queensland. We thank Dr. R. F. Evans for a sample of **1h**.

(16) Cf. Sato, M.; Ogasawara, H.; Takayama, K.; Kaneko, C. *Heterocycles* **1987**, *26*, 2611.

(17) Evidence for the existence of long-lived excited states of the ketenes is seen, particularly in the case of **4i**, which exhibits extremely strong blue phosphorescence ($\tau > 0.5$ s).

(18) Bachmann, C.; N'Guessan, T. Y.; Debu, F.; Monnier, M.; Pourcin, J.; Aycard, J.-P.; Bodot, H. *J. Am. Chem. Soc.* **1990**, *112*, 7488.

Total Synthesis of Phenanthroviridin Aglycon: The First Naturally Occurring Benzo[*b*]phenanthridine

Makarand P. Gore, Steven J. Gould,* and Dwight D. Weller

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

Received December 12, 1990

Summary: The first synthesis of a naturally occurring benzo[*b*]phenanthridine has been accomplished via coupling of a cyanophthalide and a substituted bromocinnamate and subsequent transformation of the resulting aryl naphthoquinone carboxylate via formylation, Hoffmann rearrangement, cyclization, and deprotection steps.

The isolation of the first naturally occurring benzo[*b*]-phenanthridine, phenanthroviridin (**1**), and its aglycon **2** from *Streptomyces viridiochromgenes* DSM3972 was recently reported.[1] Both compounds are active against lung carcinoma MBA9812 in mice.[1] We had previously predicted that the hypothetical pyridone **3** would be an intermediate in the transformation of dehydrorabelomycin (**4**) during the biosynthesis of the kinamycin antibiotics (kinamycin D (**5**), Scheme I).[2] It would be quite reasonable to also consider **2** as a potential intermediate in this remarkable pathway.[3,4] We now report the first synthesis of **2** by an efficient route that should also allow introduction of glycosyl moieties at the C-1 phenol for synthesis of **1** and analogues, as well as strategically placed isotopic labels for biosynthetic studies.

In order to obtain the angular tetracyclic ring system, we envisioned that the ABD rings could be constructed via coupling of a cyanophthalide with a substituted cinnamate. Cyanophthalide (**6**)[5] has been frequently used for the construction of linear tetracycles[5,6] (e.g., anthracyclinones).

(1) Fendrich, G.; Zimmermann, W.; Gruner, J.; Auden, J. A. L. Eur. Pat. Appl. EP 304,400 C1 C07D221/18), 22 Feb 1989, CH Appl. 87/3, 196, 20 Aug 1987 (*Chem. Abstr.* **1990**, *112*, 752959).

(2) Seaton, P. J.; Gould, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 5912–5914.

(3) Seaton, P. J.; Gould, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5282–5284.

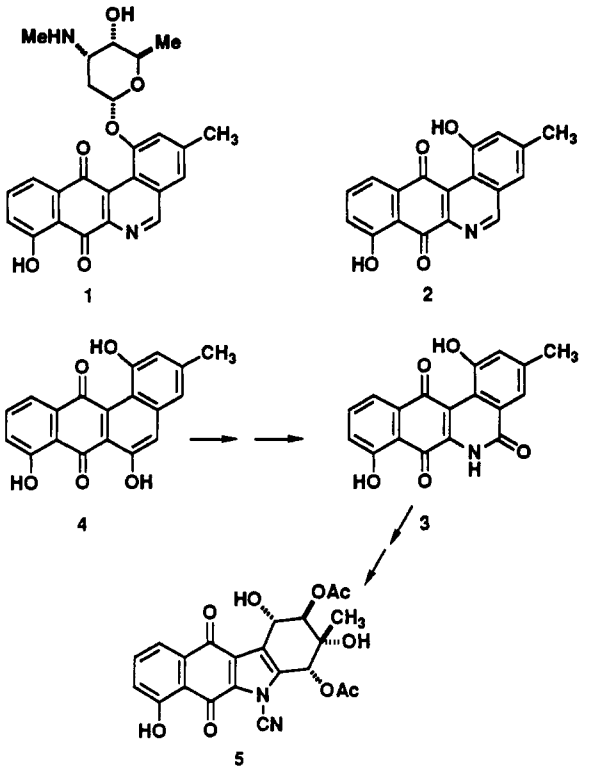
(4) Sato, Y.; Gould, S. J. *J. Am. Chem. Soc.* **1986**, *108*, 4625–4631.

(5) (a) Li, T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7009–7011. (b) Li, T.; Wu, Y. L.; Walsgrove, T. C. *Tetrahedron* **1984**, *40*, 4701–4710. (c) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805–810.

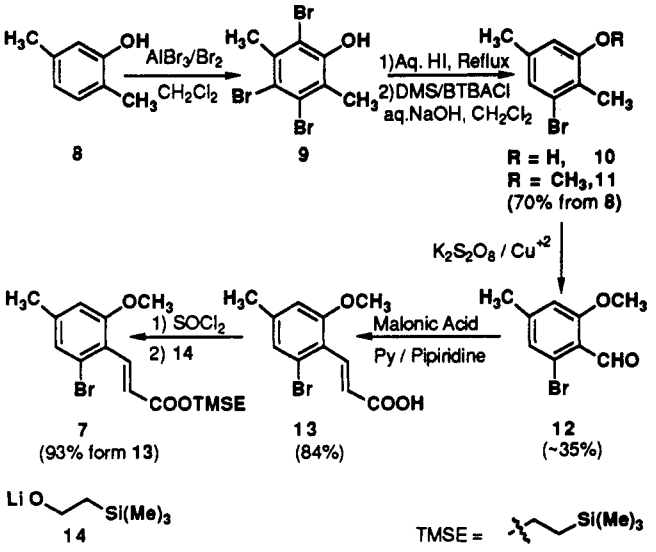
(6) (a) Russell, R. A.; Pilley, B. A.; Irvine, R. W.; Warrener, R. N. *Aust. J. Chem.* **1987**, *40*, 311–323. (b) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318–325. (c) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625–4632. (d) Kraus, Y. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Pruch, S. *J. Org. Chem.* **1983**, *48*, 3439–3446. (e) Keay, B. A.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 637–639. (f) Li, T.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *22*, 3741–3744. (g) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263–2266.

0022-3263/91/1956-2289$02.50/0

Scheme I



Scheme II



Unactivated phthalides[7] and phthalide sulfones[8] have also been used for this purpose.

To facilitate the eventual introduction of the C-5 carbon via a formylation reaction, the bromocinnamate **7** was synthesized as shown in Scheme II. 2,5-Dimethylphenol (**8**) was perbrominated[9] to **9** and then treated with hydriodic acid[10] to give the monobromide **10**. Methylation of the phenol with dimethyl sulfate under phase-transfer conditions gave **11** in 70% overall yield.[11] Although previously we have efficiently oxidized the debromo analogue of **10** to the 2-formyl derivative,[12] the presence of the bromine now proved troublesome. Treatment of **11** with $K_2S_2O_8/CuSO_4$ in aqueous acetonitrile gave erratic results (9–35% yields), while cerric ammonium nitrate[13] (23% yield) and silver(II) oxide[14] (10% yield) were even less effective, and chromyl chloride[15] failed to give any aldehyde. However, inclusion of pyridine in the persulfate/Cu^{2+} oxidation mixture[16] consistently gave 30–35% of the desired **12**. Knoevenagel condensation of **12** with malonic acid[17] gave the cinnamic acid **13** in 84% yield. Conversion to the acid chloride and treatment with the lithium alkoxide **14**[18] afforded the target **7** in 93% yield.

The synthesis of **2** was effected as shown in Scheme III. The lithium anion of **6** was generated in standard fashion, and the cinnamate **7** in THF was added at −78 °C. After being warmed to room temperature, the mixture was stirred for 20 h and then worked up to give a 68% yield of the naphthoquinone **15**.[19] This compound was reduced and methylated in situ[20] ($Na_2S_2O_4$/dimethyl sulfate/K_2CO_3) in acetone at reflux for 24 h, giving **16** in 77% yield. The ester was quantitatively deprotected with tetrabutylammonium fluoride[21] in THF and then converted to the amide **17** by treatment with Tf_2O/pyridine followed by ammonia (80% yield). The amide was now metalated (2.5 equiv of *t*-BuLi) and the anion was quenched with DMF[22] to give an 80% yield of a 1:1 mixture of the desired aldehyde **18** and the debrominated **19** along with fluorenone **20** (3%). Although **18** and **19** could be readily separated from **20** by chromatography but not from each other,[23] this was not a problem in the next steps.

(7) (a) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesure, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984–2995. (b) Graybill, T. L.; Pal, K.; McGuire, S. M.; Brobst, S. W.; Townsend, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 8306–8308. (c) Townsend, C. A.; Whittamore, P. R. O.; Brobst, S. W. *J. Chem. Soc., Chem. Commun.* **1988**, 726–728. (d) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575–7577. (e) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923–3924. (f) Townsend, C. A.; Davis, S. G.; Christensen, S. G.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885–6888. (g) Dodsworth, D. J.; Calcagno, M. P.; Ehrmann, E. U.; Bhatt, D.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2120–2124. (h) Sammes, P. G.; Dodsworth, D. J. *J. Chem. Soc., Chem. Commun.* **1979**, 33–34. (i) Brown, N. J. P.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162–164.

(8) (a) Bates, M. A.; Sammes, P. G.; Thomson, G. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3037–3045. (b) Hauser, F. M.; Hewawasam, P.; Mai, D. *J. Am. Chem. Soc.* **1988**, *110*, 2919–2924. (c) Russell, R. A.; Irvine, R. A.; Warrener, R. N. *J. Org. Chem.* **1986**, *51*, 1595–1599. (d) Tatsuta, K.; Akimoto, K.; Annaka, M. L.; Ohno, Y.; Kinoshita, M. *J. Antibiot.* **1985**, *38*, 680–682. (e) Parker, K. A.; Koziski, K. A.; Breault, G. *Tetrahedron Lett.* **1985**, *26*, 2181–2182. (f) Brade, W.; Vasella, A. *Helv. Chim. Acta* **1984**, *72*, 1649–1657. (g) Russell, R. A.; Krauss, A. S.; Warrener, R. N.; Irvine, R. W. *Tetrahedron Lett.* **1984**, *25*, 1517–1520. (h) Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1982**, *47*, 383–384. (i) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378–6386. (j) Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1981**, 108–110. (k) Dolson, M. F.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263–5264. (l) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061–3068. (m) Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1979**, *44*, 2596–2598. (n) Hauser, F. M.; Rhee, R. P.; Prasanna, S. *J. Org. Chem.* **1978**, *43*, 178–180. (o) Kraus, G. A.; Sugimoto, H. *Synth. Commun.* **1977**, *7*, 505–508.

(9) Carvalho, C. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1613–1620.

(10) Brittain, J. M.; de la Mare, P. B. D.; Newman, P. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 32–41.

(11) Satisfactory analyses and spectroscopic data were obtained for all new compounds.

(12) Hauser, F. M.; Ellenberger, S. R. *Synthesis* **1987**, 723–724.

(13) Tom, S.; Tanaka, H.; Inokuchi, T.; Nakane, S.; Akada, M.; Saito, N.; Sirakawa, T. *J. Org. Chem.* **1982**, *47*, 1647–1652.

(14) Syper, L. *Tetrahedron Lett.* **1967**, 4193–4198.

(15) Hartford, W. H.; Darin, M. *Chem. Rev.* **1958**, *1*, 1–61.

(16) Bhatt, M. V.; Perumal, P. T. *Tetrahedron Lett.* **1981**, 2605–2608.

(17) Jones, G. *Org. React.* **1967**, *15*, 204–599.

(18) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198–1199.

(19) Hauser has coupled a phthalide sulfone with a coumarin to yield a naphthoquinone derivative in the key step of a synthesis of chartreusin aglycon. Hauser, F. M.; Combs, D. W. *J. Org. Chem.* **1980**, *45*, 4071–4073.

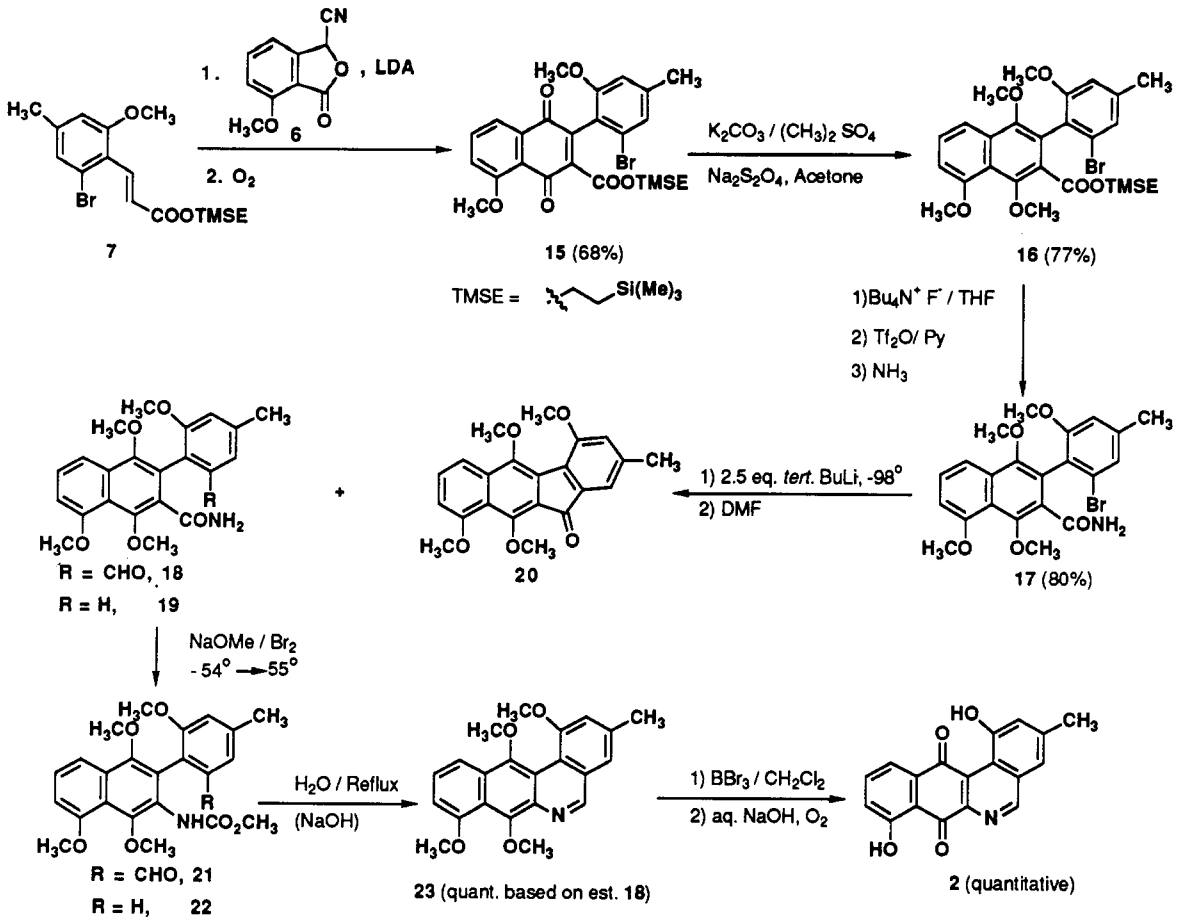
(20) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798–799.

(21) Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039–3044.

(22) Mills, R. J.; Horvath, R. F.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1145–1148.

(23) We had previously prepared **19** and **22** unambiguously from a debromocinnamate.

Scheme III



By use of modified Hoffmann rearrangement conditions[24] (NaOMe, Br_2, MeOH), the mixture of **18** and **19** yielded the carbamates **21** and **22**, while quenching this reaction with water and in situ heating at reflux for 30 min led to exclusive hydrolysis and cyclization of **21** to give **23**. Workup by acidification with dilute HCl and extraction into ethyl acetate separated **23** from **22**.[25] A quantitative yield of **23** was obtained; **22** had previously been obtained in 82% yield from pure **19**.[23,30] Finally, deprotection with BBr_3 in CH_2Cl_2 at −78 °C and warming to room temperature followed by addition of aqueous sodium hydroxide at room temperature and then bubbling O_2 through the mixture afforded **2** (quantitative), which was identical with an authentic sample of phenanthroviridin aglycon.

The route used to prepare **2** in principle can be modified to also synthesize both dehydrorabelomycin (**3**) and the pyridone **4**.[34] In each case, a C-13 label could be introduced in the formylation step in order to examine whether this carbon, indeed, becomes the cyanamide carbon of the kinamycins.[2] Efforts toward these objectives will be reported in due course.

Acknowledgment. This work was supported by U.S. Public Health Service Grant GM 31715 to S.J.G. Dr. Gabriele Fendrich, Ciba-Geigy Pharma Biotechnology, Basel, Switzerland, is thanked for an authentic sample of phenanthroviridin aglycon and data for its spectroscopic characterization. The multinuclear Bruker AC 300 NMR spectrometer was purchased through grants from the Public Health Service Division of Research Resources (RR04039-01) and the National Science Foundation (CHE-8712343) to Oregon State University. The multinuclear Bruker AM 400 NMR spectrometer was purchased in part through grants from the National Science Foundation (CHE-8216190) and from the M. J. Murdock Charitable Trust to Oregon State University.

(24) Radlick, P.; Brown, L. R. *Synthesis* **1974**, 290–292.

(25) Although benzo[*c*]phenanthridines are well-known[26] and have been synthesized numerous times,[26,27] only two previous syntheses of the benzo[*b*]phenanthridine nucleus have been described.[28,29]

(26) (a) Preininger, V. Chemotaxonomy of the Papaverareae and Fumariaceae. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 29, Chapter 1, pp 1–98. (b) Santavy, F. Papaveraceae Alkaloids I. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, Chapter 4, pp 385–545. (c) Santavy, F. Papaveraceae Alkaloids. I. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1970; Vol. 12, Chapter 5, pp 333–454. (d) Manske, R. H. F. α-Naphthaphenanthridine Alkaloids. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1968; Vol. 10, Chapter 9, pp 484–489.

(27) (a) Ninomiya, F.; Nairo, T. *Recent Dev. Chem. Nat. Carbon Compd.* **1984**, *10*, 9–90. (b) Phillips, S. D.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 223–232. (c) Phillips, S. D.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 223–232. (d) Ninomiya, F.; Yamamoto, O.; Kiguchi, T.; Naitro, T.; Ishii, H. *Heterocycles* **1977**, *6*, 1730–1734. (e) Snieckus, V. A. *Alkaloids* **1972**, *2*, 185–198. (f) Whaley, W. M.; Meadow, M. *J. Org. Chem.* **1954**, *19*, 661–665.

(28) Gensler, W. J.; Vinovskis, M.; Wang, N. *J. Org. Chem.* **1969**, *34*, 3664–3666.

(29) Klemm, L. H.; Weisert, A. *J. Heterocycl. Chem.* **1965**, *2*, 15–20.

(30) We were unsuccessful in cyclizing **22** to the D ring under either photochemical[31] or modified Bischler–Napieralski conditions.[32,33]

(31) Yang, N. C.; Shani, A.; Lenz, G. R. *J. Am. Chem. Soc.* **1966**, *88*, 5369.

(32) Kametani, T.; Ohsawa, T.; Ihara, M.; Fukumoto, K. *Chem. Pharm. Bull.* **1978**, *26*, 1922–1926.

(33) Nagubundi, S.; Fodor, G. *Heterocycles* **1981**, *15*, 165–177.

(34) We have also prepared the phenol corresponding to **7**. Selective protection (e.g., other than methoxyl) should allow synthesis of C-1 *O*-glycosides, such as **1** or its analogues.