N-4 protons in urazole are similar, and that the amide N-1 proton in 1-methylurazole is about 0.5 pK units more acidic than the imide N-4 proton contained in that species. We are less certain of the relative DMSO-phase acidities of the amide and imide protons in 1-phenylurazole. An assumption that the ratio of the acidifying effect of a 4-phenyl substituent (on an amide proton) to the acidifying effect of a 1-phenyl substituent (on an imide proton) will be similar to what was observed in the case of 4-methyl and 1-methyl substituents (where the 4-methyl substituent acidifies the amide proton by 0.8 pK units, while the 1-methyl substituent acidifies the imide proton by ca. 0.4 pK units, a ratio of 2:1) leads to the prediction that the pK_a of the imide proton in 1-phenylurazole is about 12. Comparison of the measured acidity constant for the amide proton in 1-phenylurazole (pK_a = 9.9) with the estimate for the imide NH acidity constant in 1-phenylurazole suggests that the difference in the acidity constants for the two protons in 1-phenylurazole is about 2 orders of magnitude, a difference that agrees nicely with Katritzky's estimates for the relative acidities of these protons in water.[3]

In further attempts to better understand structural features of the monoanions derived from urazoles **1–12**, we are presently engaged in NMR and UV spectroscopic investigations of these species. Also underway are studies of the homolytic strengths of amide and imide N–H bonds in urazole and substituted urazoles, and studies of the acidities and stabilities of the incipient urazolyl radicals. Preliminary results indicate that the N-1–H (amide) bond in urazole is ca. 15 kcal/mol weaker (in a homolytic sense) than the N-4–H (imide) bond in the same species.[10]

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the United States Army Research Office (Contract No. DAAL-03-90-G-0046), and the Southern Illinois University Materials Technology Center for support of this work.

(10) Bausch, M. J.; David, B.; Prasad, V.; Vaughn, A. *J. Phys. Org. Chem.*, submitted for publication.

Stereoselective Oxidative Spiroketalization of a *C*-Arylglucal Derived from Palladium-Catalyzed Coupling. Synthesis of the *C*-Arylglucoside Spiroketal Nucleus of the Papulacandins

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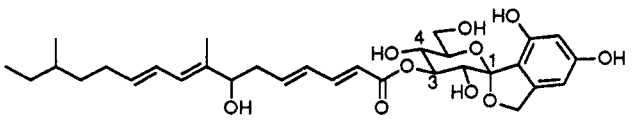
Received September 10, 1990

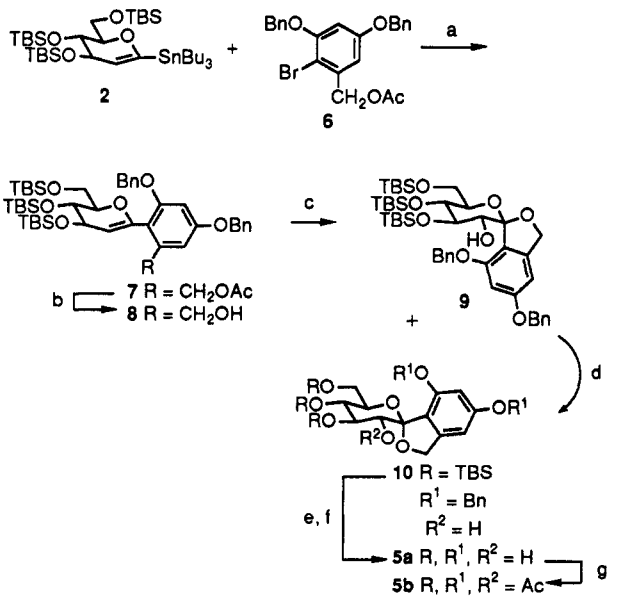
Summary: The synthesis of the *C*-arylglucoside tricyclic spiroketal nucleus of the papulacandins **5b** was achieved utilizing two key steps, namely the palladium-catalyzed coupling of the aryl bromide **6** and the stannyl glucal **2** and stereoselective oxidative spiroketalization of the derived *C*-arylglucal **7**.

There has been a great deal of interest in recent years in the synthesis of *C*-arylglycosides since many of the natural products that contain this novel structural framework exhibit antibiotic or antiviral activity.[1] In 1976, Traxler and co-workers isolated a series of four closely related antifungal antibiotics, named papulacandins A–D, from *Papularia sphaerosperma*.[2] The mechanistic basis for the inhibitory activity of papulacandin B toward the growth of the fungus *Geotrichum lactis* was traced to a penicillin-like ability to inhibit glucan synthesis during the manufacture of the cell wall.[3] Papulacandin D (**1**),[4] the simplest member of the family, illustrates the unique, and synthetically challenging, structural feature common to all



1 Papulacandin D

Scheme I[a]



[a] Reaction conditions: (a) $Pd(Ph_3P)_2Cl_2$ (5 mol %), see text for conditions; (b) LAH, Et_2O, 0 °C; (c) DMDO, CH_2Cl_2; (d) PPTS, $CHCl_3$, room temperature; (e) H_2, P on C (10%), EtOAc, 40 °C; (f) TBAF, THF, room temperature; (g) Ac_2O, py, DMAP, room temperature.

(1) Hacksell, U.; Daves, G. D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1.
(2) Traxler, P.; Gruner, J.; Auden, J. A. L. *J. Antibiot.* **1977**, *30*, 289.
(3) (a) Baguley, B. C.; Rommele, G.; Gruner, J.; Wehrli, W. *Eur. J. Biochem.* **1979**, *97*, 345. (b) Perez, P.; Varona, R.; Garcia-Acha, I.; Duran, A. *FEBS Lett.* **1981**, *129*, 249. (c) Rommele, G.; Traxler, P.; Wehrli, W. *J. Antibiot.* **1983**, *36*, 1539.

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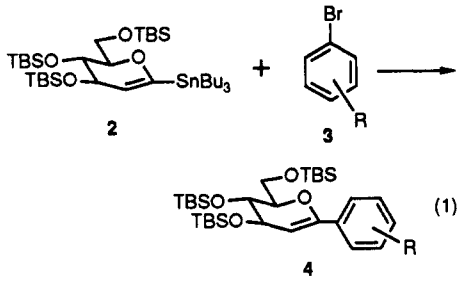
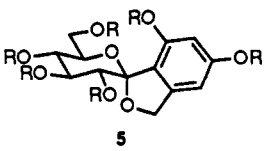
of the papulacandins. In the key substructure, a tricyclic spiroketal nucleus that consists of D-glucose and 5-(hydroxymethyl)resorcinol fragments, exhibits both α-*O*-glucosyl and β-*C*-arylglucosyl bonding patterns.

Recently, we described[5] an efficient procedure for the preparation of *C*-arylglucals **4** by the palladium-catalyzed coupling of 3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-1-(tributylstannyl)-D-glucal **2**[6] with aryl bromides **3** (eq 1).



(1)



Herein, we describe the concise and efficient synthesis of the spiroketal nucleus of the papulacandins (**5**).[7] The successful synthesis illustrates the facility with which certain *C*-arylglycosides can be accessed from the now readily available *C*-arylglucals **4** by the stereoselective oxidative functionalization of the enol ether double bond in compounds such as **4**.

The synthesis of **5** is outlined in Scheme I. The coupling of **2** and the aryl bromide **6**[8] (1.1 equiv) was effected as described previously[5] in the presence of $Pd(Ph_3P)_2Cl_2$ (5 mol %). As we had observed earlier,[5] the production of the *C*-arylglucal **7**[10] (49% in refluxing toluene for 24 h; 51% in refluxing mesitylene for 1 h) was accompanied by a significant amount of dimerized **2** (up to 20% in toluene). A useful solution to the dimerization problem was achieved by using an excess of **2** (2.1 equiv in toluene) and considering **6** as the limiting reagent. In this manner, **7** was produced in 85% yield based on **6**. Reductive deprotection of **7** (LAH, Et_2O) provided the benzyl alcohol **8** in 96% yield.

The completion of the synthesis of **5** from **8** necessitated that we effect both stereocontrolled installation of the C2 hydroxyl moiety and oxidative spiroketalization. We envisioned that these two goals could be achieved concurrently by (1) the initial stereoselective α-epoxidation of the C1–C2 enol ether double bond in **8** using dimethyldioxirane (DMDO)[11] and (2) the rapid intramolecular trapping of the initially formed α-epoxide with the benzylic hydroxyl.[12]

In the event, treatment of a CH_2Cl_2/Me_2CO solution of **8** at 0 °C with DMDO smoothly provided the chromatographically separable spiroketals **9** and **10** in a combined yield of 84% (**9**:**10** 1:5). While all previous syntheses of **5**[7] have utilized thermodynamically equilibrating conditions to effect spiroketalization, this reaction represents the first instance of stereoselective spiroketalization under nonequilibrating conditions[14] in an intramolecular Lemieux type reaction.

The C2 configuration of these isomers was confirmed by inspection of the ^1H NMR spectra of each. The spectrum of **10** in C_6D_6 displayed signal at δ 4.70 ppm ($J_{2,3}$ = 9.3 Hz) and δ 4.19 ppm ($J_{3,4}$ = 8.4 Hz) that correspond to the H2 and H3 proton resonances, respectively. The large coupling constants suggest that **10** possesses the gluco configuration and adopts a $^4C_1$ conformation wherein there are mutual trans-diaxial relationships between H2–H3 and H3–H4. It is interesting to note that the isomeric glucoside **9** prefers an alternative twisted conformation as exhibited by the magnitudes of the coupling constants between H2, H3, and H4 ($J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 4 Hz).

Although the observed 5:1 ratio of **10**:**9** could be improved to 34:1 by conducting the oxidation reaction at −78 °C, it was found that simply treating a $CHCl_3$ solution of **9** and **10** with catalytic PPTS at room temperature (3 h) effected the complete and clean isomerization of **9** to **10** (recovery yield 95%).[15] Thus, **10** is obtained in an overall yield of 80% from **8** after epimerization.

Deprotection of **10** (H_2, Pd–C, EtOAc, 40 °C; TBAF, THF) provided the synthetic papulacandin spiroketal nucleus **5a**. Acetylation (Ac_2O, py) of this highly polar material provided synthetic **5b** (three steps from **10**; 45% after recrystallization) that was identical (400-MHz ^1H NMR, TLC) with **5b** obtained from authentic **5a**[16] and was consistent with data (IR, mp, $[\alpha]_D$) reported[7b] for **5b**.

Thus, the oxidative spiroketalization of *C*-arylglucals **4** under nonequilibrating conditions in an intramolecular Lemieux type process has been demonstrated to be highly stereoselective. The concise synthesis of **5b** from **2** and **6** suggests that the synthesis of other important *C*-aryl-

(4) (a) Traxler, P.; Fritz, H.; Richter, W. J. *Helv. Chim. Acta* **1977**, *60*, 578. (b) Gruner, J.; Traxler, P. *Experimentia* **1977**, *33*, 137. (c) Rihs, G.; Traxler, P. *Helv. Chim. Acta* **1981**, *64*, 1533. (d) Traxler, P.; Fritz, H.; Fuhrer, H.; Richter, W. J. *J. Antibiot.* **1980**, *33*, 967.

(5) Friesen, R. W.; Sturino, C. F. *J. Org. Chem.* **1990**, *55*, 2572.

(6) Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926.

(7) (a) A synthesis of the racemic papulacandin spiroketal core has been reported utilizing hetero-Diels–Alder technology. Danishefsky, S.; Phillips, G.; Ciufolini, M. *Carbohydr. Res.* **1987**, *171*, 317. Two syntheses of the optically pure spiroketal cores have been described, both utilizing the addition of metalated aromatics to glucose derived electrophiles. (b) Schmidt, R. R.; Frick, W. *Tetrahedron* **1988**, *44*, 7163. (c) Rosenblum, S. B.; Bihovsky, R. *J. Am. Chem. Soc.* **1990**, *112*, 2746.

(8) **6a** was prepared in two steps (NBS, CCl_4, 70 °C, 95%;[9] Ac_2O, Et_3N, CH_2Cl_2, 99%) from 3,5-bis(benzyloxy)benzyl alcohol.[7a]

(9) Noire, P. D.; Franck, R. W. *Synthesis* **1980**, 882.

(10) All compounds reported herein exhibited spectra in full accord with structural assignments. New compounds gave satisfactory molecular mass determinations and/or combustion analyses.

(11) (a) For the first report on the use of dimethyldioxirane (DMDO) for the epoxidation of cyclic vinyl ethers, see: Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 1988. (b) Danishefsky and Halcomb have shown that the epoxidation of 3,4,6-tri-*O*-(*tert*-butyldimethylsilyl)-D-glucal with DMDO is stereospecific, providing the isolable α-epoxide. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661. In the Danishefsky synthesis of **5**,[7a] epoxidation of a *C*-arylglucal (mCPBA, MeOH) provided an anomeric mixture of methyl glucosides.

(12) Recent observations by Danishefsky[11b] suggest that β-D-glucosides could be expected as the kinetic products of α-epoxide opening. However, in the classic Lemieux synthesis of sucrose and related disaccharides (Lemieux, R. U.; Huber, G. *J. Am. Chem. Soc.* **1953**, *75*, 4118 and Lemieux, R. U.; Huber, G. *J. Am. Chem. Soc.* **1956**, *78*, 4117) an α-D-glucoside is produced by the intermolecular reaction of a hydroxyl nucleophile with Brigl's anhydride.[13] Although acetate protecting groups are used in the Lemieux synthesis, by mechanistic analogy, intramolecular opening of the α-epoxide derived from **8** might be expected to occur in the desired stereochemical sense via an intermediate oxonium ion.

(13) Brigl, P. *Z. Physiol. Chem.* **1922**, *122*, 245.

(14) No isomerization of **9** to **10** was observed upon exposure of pure **9** to DMDO under the conditions of the original reaction.

(15) This result is in contrast to a previous report[7c] which documents the inability to effect acid-catalyzed anomerization in a related system.

(16) Authentic hexaacetate **5b** was prepared (Ac_2O, py) from a sample of **5a** obtained from degradation of the papulacandins. We would like to thank Drs. R. Scartazzini and K. Scheibli of Ciba-Geigy, Basel, for kindly providing us with a sample of **5a**.

glycosides can be achieved from similar *C*-arylglycal precursors. These possibilities are currently being explored.

Acknowledgment. We gratefully acknowledge the Natural Sciences and Engineering Research Council of Canada and the University of Toronto for financial support and the University of Toronto for an Open Fellowship (to C.F.S.).

Supplementary Material Available: Physical constants and spectral data for **6–10** and **5b** (2 pages). Ordering information is given on any current masthead page.

Selective Control of the Various Cycloaddition Products from Reactions of Styrenes and 1,4-Benzoquinones: Optimization of the Formal 5 + 2 Cycloadducts

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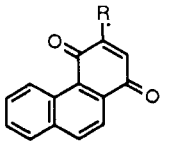
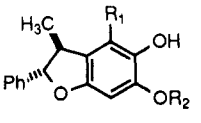
Received August 20, 1990

Summary: 7-Aryl-3-hydroxy-6-methylbicyclo[3.2.1]oct-3-ene-2,8-diones **4** and **8** are formed exclusively in Ti(IV)-catalyzed reactions of 2-((4-methoxybenzyl)oxy)-1,4-benzoquinones **5a/d** with *trans*-β-methylstyrene and indene, respectively.

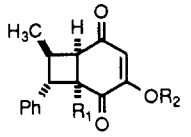
An important issue in the development of synthetically useful reactions is whether or not a single desired product can be obtained selectively in good yield from systems in which several reaction pathways are available. Such is the situation encountered in reactions of styrenes and 1,4-benzoquinones in which, among other processes,[1] as many as four different products of formal cycloaddition[2] can be obtained depending upon reaction conditions. Diels–Alder adducts **1** (4 + 2 cycloadducts) are found under thermal conditions.[3] With Lewis acid catalysis, *trans*-β-methylstyrenes and 2-alkoxy-1,4-benzoquinones produce the dihydrobenzofurans **2** (formal 3 + 2 cycloadducts), the bicyclo[4.2.0]oct-3-ene-2,8-diones **3** (2 + 2 cycloadducts), and/or the bicyclo[3.2.1]oct-3-ene-2,8-diones **4** (5 + 2 cycloadducts).[4] In many cases it is possible to form selectively either the 3 + 2 or 2 + 2 cycloadduct by proper choice of reaction conditions.[4a,c] Herein, we report for the first time a simple variant of the system which results in the direct, exclusive formation of the formal 5 + 2 adducts **4** in good yield. Thus, these reactions provide direct access to biologically important neolignans incorporating the 7-arylbicyclo[3.2.1]octene skeleton as well as the 2-aryl-2,3-dihydrobenzofuran framework and oxidized derivatives.[5]



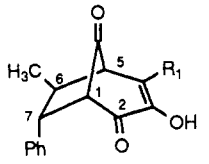
1, R=H, CH_3 or OCH_3



2, R_1=H or CH_3, R_2=CH_3



3, R_1=H or CH_3, R_2=CH_3



4a, R_1=CH_3
4b, R_1=H

The formation of **2**–**4** can be rationalized via intermediates **6** and **7** (Scheme I) which may result from a ($4\pi + 2\pi$) cycloaddition of the Ti(IV)–quinone complex with the styrene to give **6** directly[6] followed by ring opening to **7** (path a). Alternately, **7** may be formed by a stereoselective alkylation of the Ti(IV)–quinone complex by the styrene. Ring closure of **7** via path b gives **6**, and dealkylation of **6** by chloride ion present in the reaction mixture ultimately yields **4** (path c). Bond formation between the carbocation center in **7** and the titanium enolate moiety or the carbonyl group followed by loss of a proton produces **3** and **2**, respectively.[7] In any event,[8] we reasoned that a controlling

(1) Additional reaction manifolds involve hydride or hydrogen atom abstraction processes: (a) Lee-Ruff, E.; Ablenas, F. J. *Can. J. Chem.* **1989**, *67*, 699. (b) Takada, M.; Oshima, R.; Yamauchi, Y.; Kumanotani, J.; Seno, M. *J. Org. Chem.* **1988**, *53*, 3073. For a recent review, see: (c) Becker, H.-D.; Turner, A. B. In *The Chemistry of Quinonoid Compounds, Vol. 2*; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: New York, 1988; p 1351.

(2) For a recent review, see: Finley, K. T. in ref 1c, p 537.

(3) (a) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Tamura, O. *Tetrahedron Lett.* **1989**, *30*, 3995. (b) Manning, W. B. *Ibid.* **1981**, *22*, 1571. (c) Kelly, T. R.; Magee, J. A.; Weibel, F. R. *J. Am. Chem. Soc.* **1980**, *102*, 798. (d) Rosen, B. I.; Weber, W. P. *J. Org. Chem.* **1977**, *42*, 3463. (e) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 563. (f) Lora-Tamayo, M. *Tetrahedron* **1958**, *4*, 17. (g) For a review, see: Wagner-Jauregg, T. *Synthesis* **1980**, 769 and references cited in the above.

(4) (a) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931. (b) Engler, T. A.; Combrink, K. D.; Takusagawa, F. *J. Chem. Soc., Chem. Commun.* **1989**, 1573. (c) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Vander Velde, D. *J. Org. Chem.* **1990**, *55*, 1248 and references cited therein.

(5) For recent reviews and leading references on the pharmacological activity of neolignans, see: (a) Gottlieb, O. R. In *New Natural Products and Plant Drugs with Pharmacological, Biological or Therapeutic Activity*, Proceedings of the First International Congress, 1976; Wagner, H., Wolff, P. M., Eds.; Springer Verlag: Berlin, 1977; p 277. (b) Gottlieb, O. R. *Quim. Nova* **1984**, *7*, 250. For current reviews on the isolation, chemistry, and synthesis of lignans and neolignans, see: (c) Gottlieb, O. R. *Fortsch. Chem. Org. Naturst.* **1978**, *35*, 1. (d) Gottlieb, O. R. *Rev. Latinoamer. Quim.* **1974**, *5*, 1. (e) Gottlieb, O. R. *Phytochemistry* **1972**, *11*, 1537. (f) Ward, R. S. *Chem. Soc. Rev.* **1982**, *11*, 75. (g) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191. (h) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499.

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