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Studies on the Synthesis of Furanosteroids. I. Viridin Models

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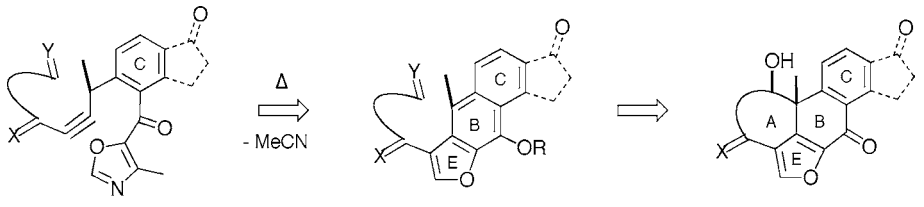
ABSTRACT



I II III

Alkyne oxazoles of general structure I are transformed directly to furo[2,3-*b*]phenol derivatives II by a sequence involving intramolecular Diels–Alder/retro-Diels–Alder reaction followed by tautomerization. Suitably functionalized phenols II undergo an intramolecular phenol–dienone–aldol condensation, generating the A,B,E-ring skeleton III characteristic of the viridin (1) class of furanosteroids.

The furanosteroids are a class of novel pentacyclic fungal metabolites that share in common a furan ring, bridging positions 4 and 6 of the steroid skeleton (Figure 1).[1] Members of this class have attracted attention for many years because of their potent antiinflammatory and antibiotic properties[2a] and more recently because of their ability to selectively block certain intracellular signaling pathways associated with cell growth and development.[2b,c] As such, they have potential as new therapeutic agents for diseases characterized by rapid cell proliferation, including cancer. Prominent members include those of the viridin (**1**) and wortmannin (**2**) families, which owe their growth inhibitory properties to their activity as irreversible inhibitors of phosphoinositide 3-kinase (PI3K),[1] a class of enzymes that play a key role in important cell signaling processes.[2b,c] Structure−activity studies have identified C_{20} in both **1** and **2** as a crucial site for PI3-kinase inhibition, most likely due to the highly electrophilic nature of the furan ring.[2d] It has been postulated that irreversible inhibition occurs by nucleophilic addition of the kinase to C_{20} (arrows),[2e] a process that is facilitated by the C_3 and C_7 carbonyl groups. In vitro studies support this premise because both amines and thiols rapidly open the furan ring.[2d]

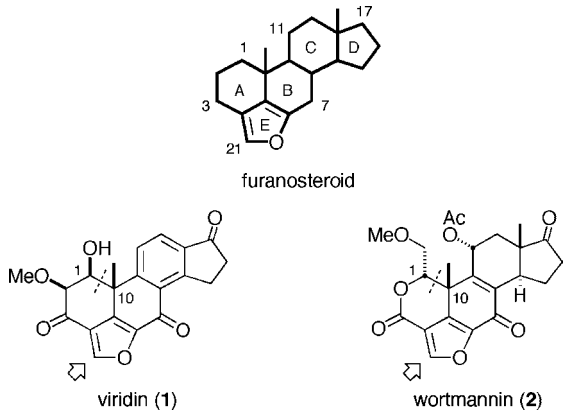


Figure 1. Furanosteroid class of PI3-kinase inhibitors.

(1) For reviews, see: (a) Hanson, J. R. *Nat. Prod. Rep.* **1995**, *12*, 381. (b) Wipf, P.; Halter, J. H. *Org. Biomol. Chem.* **2005**, *3*, 2053.

(2) (a) Brian, P. W.; McGowan, J. C. *Nature (London)* **1945**, *156*, 144. (b) Powis, G.; Bonjouklian, R.; Berggren, M. M.; Gallegos, A.; Abraham, R.; Ashendel, C.; Zalkow, L.; Matter, W. F.; Dodge, J. *Cancer Res.* **1994**, *54*, 2419. (c) Ward, S.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, F. *Chem. Biol.* **2003**, *10*, 207 and cited references. See also 1b. (d) Norman, B. H.; Shih, C.; Toth, J. E.; Ray, J. E.; Dodge, J. A.; Johnson, D. W.; Rutherford, P. G.; Schultz, R. M.; Worzalla, J. F.; Vlahos, C. J. *J. Med. Chem.* **1996**, *39*, 1106. (e) Wymann, M. P.; Bulgarelli-Leva, G.; Zvelebil, M. J.; Pirola, L.; Vanhaesebroeck, B.; Waterfield, M. D.; Panatotou, G. *Mol. Cell. Biol.* **1996**, *16*, 1722. (f) Liu, Y.; Shreder, K. R.; Gai, W.; Corral, S.; Ferris, D. K.; Rosenblum, J. S. *Chem. Biol.* **2005**, *12*, 5256.

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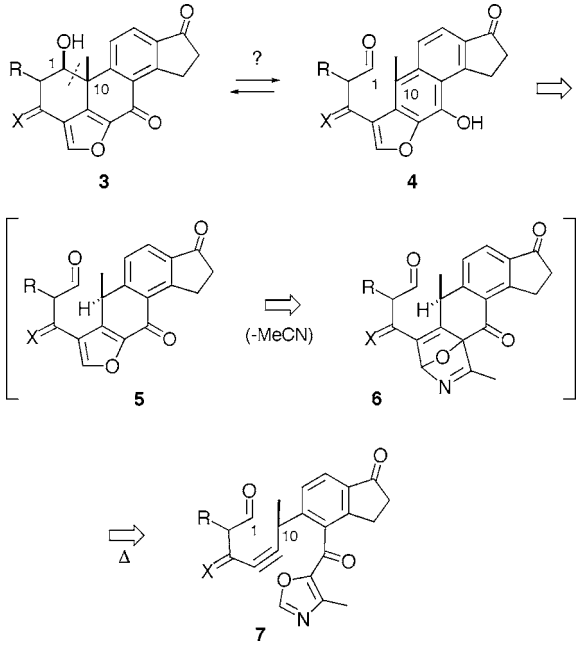
However, only a small number of analogues have been successfully prepared to test this hypothesis in vivo.

Progress in this area has been slow because of the many difficulties associated with synthesizing these compounds.[3] Despite efforts spanning over two decades, only one very recent total synthesis of **1** has been reported,[3m] along with two syntheses of **2** (one de novo).[3b,d] The furanosteroid skeleton itself has also proven to be a significant synthetic challenge. Recently, we began a program exploring a fundamentally new approach to synthesizing members of the viridin (**1**) and wortmannin (**2**) families, involving bond disconnection at C_1-C_{10} (cf. dashed lines in Figure 1). Our synthetic analysis for viridin and related furanosteroids is shown in Scheme 1.

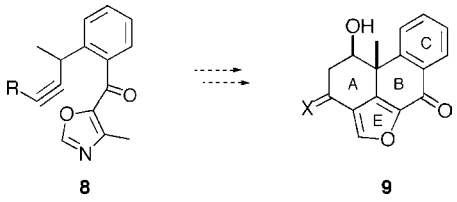
Scheme 1. Viridin Synthetic Analysis



A distinguishing feature of the viridin skeleton **3** is that the C_1-C_{10} bond can be *formally* derived by intramolecular aldol condensation of phenol aldehydes **4** (Scheme 1; *not* the biogenetic pathway). Viewed in this context, it is interesting that **3** and related materials do not at least partly revert to **4** via retro-aldol reaction, providing a pathway for C_1-epimerization. However, to the best of our knowledge, the C_1 α-epimer of **3** does not occur naturally. On this basis, we reasoned that if such an equilibrium exists it must strongly favor the ring-closed product **3** as well as the "natural" syn stereochemistry at C_1-C_{10}. It followed that **4** constituted an attractive synthetic precursor to **3**.

In our synthetic planning, we assumed that the phenol ring in **4** has little aromatic character, analogous to the case with anthracen-10-ol and related species.[4] Otherwise, it would be difficult to rationalize the stability of compounds such as **3**. Also, in the transformation of **4** to **3**, we expected that the desired syn stereochemistry at C_1-C_{10} would predominate under kinetic control due to a more favorable Burgi−Dunitz trajectory angle (vide infra).[5] The overriding issue pertained to the synthesis of **4** itself, which we hoped to accomplish employing the alkyne oxazole Diels−Alder (DA) methodology we have used in the syntheses of numerous naturally occurring furans, butenolides, and lactones.[6] Thus, DA/retro-DA reaction of **7** was expected to lead directly to furan **5**, which upon tautomerization would afford the desired phenol **4** (Scheme 1). To test this approach, we have been investigating the synthesis and reactivity of simpler alkyne oxazoles of type **8**, focusing on their conversion to viridin model systems **9** incorporating the characteristic skeletal features of **1** (Scheme 2).

Scheme 2. Proposed Viridin Model Studies



We pursued a number of routes for the synthesis of alkyne oxazoles **8**. Ultimately, however, we made use of the innovative methodology of Pettus et al., who developed a general procedure for converting salicylaldehyde derivatives to a wide variety of o-substituted phenols.[7a] This is illustrated in Scheme 3 for the parent compound **10**, which in step 1 is converted to the Boc derivative **11**. Next, in a very efficient sequence, treatment of **11** with 1.05 equiv of MeLi generated the reactive *o*-quinone methide **12**, by a pathway involving nucleophilic addition to the aldehyde, followed by intramolecular transfer of the Boc group and 1,4-elimination (not shown). Quenching with the Grignard reagent derived from trimethylsilylacetylene (TMSA) followed by triflation then gave a 74% overall yield of the desired triflate derivative **14** on 95 mmol scales (>20 g). With ample quantities of **14**

(3) Representative studies. *Wortmannin family*: (a) Broka, C. A.; Ruhland, B. *J. Org. Chem.* **1992**, *57*, 4888. (b) Sato, S.; Nakada, M.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 6141. (c) Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311. (d) Mizutani, T.; Honzawa, S.; Tosaki, S.-y.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4680. (e) Wipf, P.; Halter, R. J. *Org. Biomol. Chem.* **2005**, *3*, 2053 and cited references. *Viridin family*: (f) Moffatt, J. S. *J. Chem. Soc. (C)* **1966**, 734. (g) Yasuchika, Y.; Kenji, H.; Kanematsu, K. *Chem. Commun.* **1987**, 515. (h) Carlina, R.; Higgs, K.; Older, C.; Randhawa, S.; Rodrigo, R. *J. Org. Chem.* **1997**, *62*, 2330. (i) Souza, F. E. S.; Rodrigo, R. *Chem. Commun.* **1999**, 1947. (j) Boynton, J.; Hanson, J. R.; Kiran, I. *J. Chem. Res. (S)* **1999**, 638. (k) Wright, D.; Whitehead, C.; Orugunty, R. *Abstracts of Papers*, 221st ACS National Meeting, 2001; American Chemical Society: Washington, DC. (l) Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943. (m) Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1998.

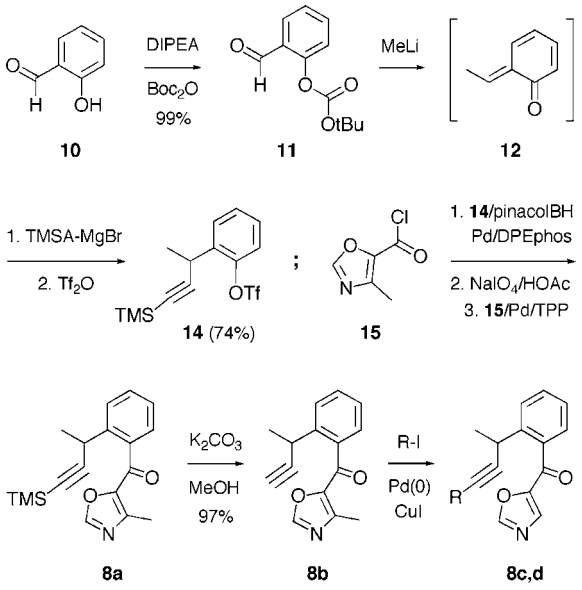
(4) Freiermuth, B.; Hellrung, B.; Peterli, S.; Schultz, M.-F.; Wintgens, D.; Wirz, J. *Helv. Chim. Acta* **2001**, *84*, 3796.

(5) Burgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

(6) For leading references, see: Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295.

(7) (a) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*(27), 6502. (b) We are grateful to Mr. Roger O'Connor of these laboratories for optimizing this step.

Scheme 3. Synthesis of Model Alkyne Oxazoles **8**



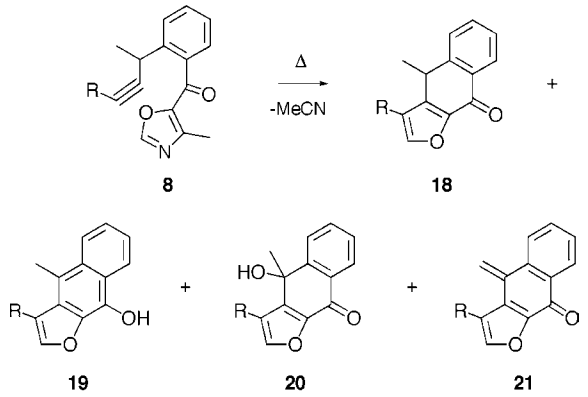
c) R = *cis*-HC=CHCO$_2$Et. **d**) R = Ph.

in hand, we developed a straightforward three-step sequence leading to the alkyne oxazole **8a**, consisting of (1,2) elaboration to the corresponding boronic acid **17** (not shown)[7b] and (3) Suzuki coupling with the readily prepared acid chloride **15** (average yield ~ 80% per step). Finally, for the purpose of additional functionalization, the initially produced TMS−alkyne **8a** was desilylated to **8b** with K_2CO_3/MeOH (97%). Among other examples, this last material then afforded alkyne oxazoles **8c**,**d** using standard coupling techniques.

Upon thermolysis (140−170 °C), alkyne oxazoles **8a**−**d** were converted to variable mixtures of four Diels−Alder derived products, identified as dienones **18**, phenols **19**, and the oxidized products **20** and **21** (28−67% combined yields, not optimized).[8] A detailed study of this reaction provided information on the source of each compound. As expected, dienones **18** are the primary reaction products, and they are reasonably stable in the absence of air or acid impurities. On acidic workup, however, dienones **18** undergo equilibration with the corresponding phenols **19**, which proved to be extremely sensitive to oxidation even at ambient temperature. This conversion produced directly the tertiary alcohols **20**, which on thermolysis gave the quinone methides **21**. Initially, we were surprised to find that tautomers **18** survived the reaction conditions. However, a search of the literature revealed that this phenomenon is quite common, as, for example, in various furanoeremophilanes isolated from the *Psacalium* and *Senecio* genera.[9a−c] Most likely, such tautomers are also stabilized by relief of *peri*-interactions. In any event, this finding gave us additional confidence that the eventual closure of ring A would be thermodynamically favored.

Our viridin model studies made use of the alkyne oxazole **8c** (Scheme 4, R = *cis*-HC=CHCO$_2$Et), which was prepared in 63% yield by Sonogashira coupling of **8b** (R = H) with ethyl *cis*-iodoacrylate.[9d] Upon heating in *o*-xylene (140 °C),

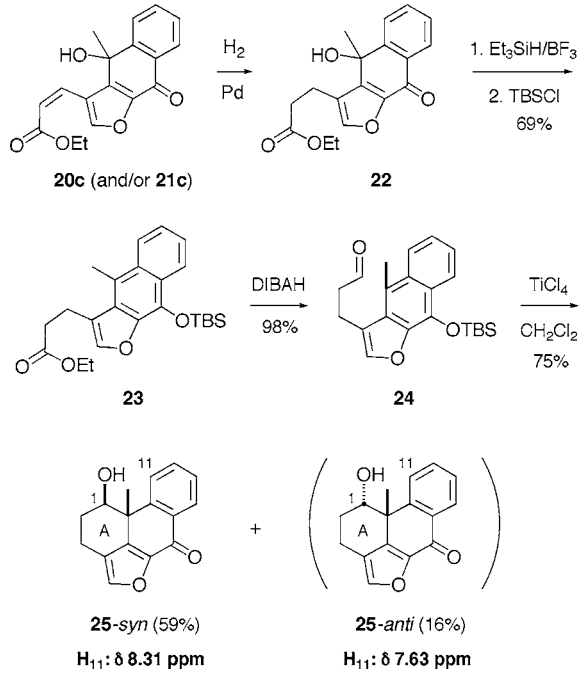
Scheme 4. Preliminary Thermolysis Studies



a) R = TMS. b) R = H. **c**) R = *cis*-HC=CHCO$_2$Et. **d**) R = Ph.

8c was transformed to a mixture of **18c**−**21c**, in a combined yield of 59% at 73% conversion (cf. Scheme 4). The formation of **20c** and **21c** could be lessened by thorough degassing and employing antioxidants. Usually, though, we found it expeditious to allow oxidation to proceed because both **20c** and **21c** functioned as convenient and stable sources of the parent phenol **19** and related derivatives. For example, employing **20c**, we were able to prepare the saturated ester derivative **23** by a simple two-step sequence consisting of catalytic hydrogenation (**20c** → **22**),[8] followed by regeneration of the parent phenol (Et_3SiH, BF_3·Et_2O) and in situ silylation (Scheme 5). The identical sequence could be

Scheme 5. Preparation of a Viridin (**1**) Model



applied with equal efficiency to mixtures of **20c** and **21c**. DIBAH reduction of **23** then afforded a nearly quantitative

yield of aldehyde **24**, which was a suitable substrate for testing the formation of ring A. Having at this point reached the "moment of truth", we were pleased to find that **24** cleanly underwent the desired ring closure, producing with $TiCl_4/CH_2Cl_2$ a 75% yield of viridin models **25**-*syn* and **25**-*anti* with 4:1 stereoselectivity. Under these conditions, no evidence was found for equilibration between **25**-*syn* and **25**-*anti* nor for retro-aldol cleavage to give back **24**.

We took special care in assigning the structures of **25**-*syn* and **25**-*anti* because this transformation strongly supports the viability of our proposed syntheses of viridin (**1**) and related species. In addition to detailed NOE studies, which fully corroborated the structure of **25**-*syn*, the isomeric alcohols **25**-*syn* and **25**-*anti* have a tell-tale signature in their NMR spectra not previously described (Figure 2; cf. also Supporting Information). As in viridin (**1**) itself, H_{11} in **25**-*syn* resides in the deshielding zone of the C_1-hydroxyl group (nearly coplanar), and it's signal is shifted dramatically downfield (8.31 ppm). In contrast, the corresponding signal in **25**-*anti* is found at 7.63 ppm. A nearly identical chemical shift difference is observed for H_{11} in the closely related epimeric alcohols **26**-*syn* and **26**-*anti*, prepared by Sorensen et al. in their synthesis of **1**.[3m,10] Finally, acylation of **25**-*syn* gave a crystalline acetate derivative **25**-*syn*-*Ac*, whose structure was confirmed by X-ray analysis.[8]

We are confident the conversion of **24** to **25**-*syn* can be optimized to both higher yields and selectivities, and we expect ultimately to effect transformations of the type **7** → **3** in a single step (cf. Scheme 1). Total syntheses of **1** and **2** employing this methodology are under investigation.

Acknowledgment. E.H.S. (Dartmouth College) was the recipient of a National Science Foundation Predoctoral Fellowship during portions of this work.

Supporting Information Available: Experimental and NMR spectra for all new compounds. X-ray crystal structures for **22** and **25**-*syn*-*Ac*. This material is available free of charge via the Internet at http://pubs.acs.org.

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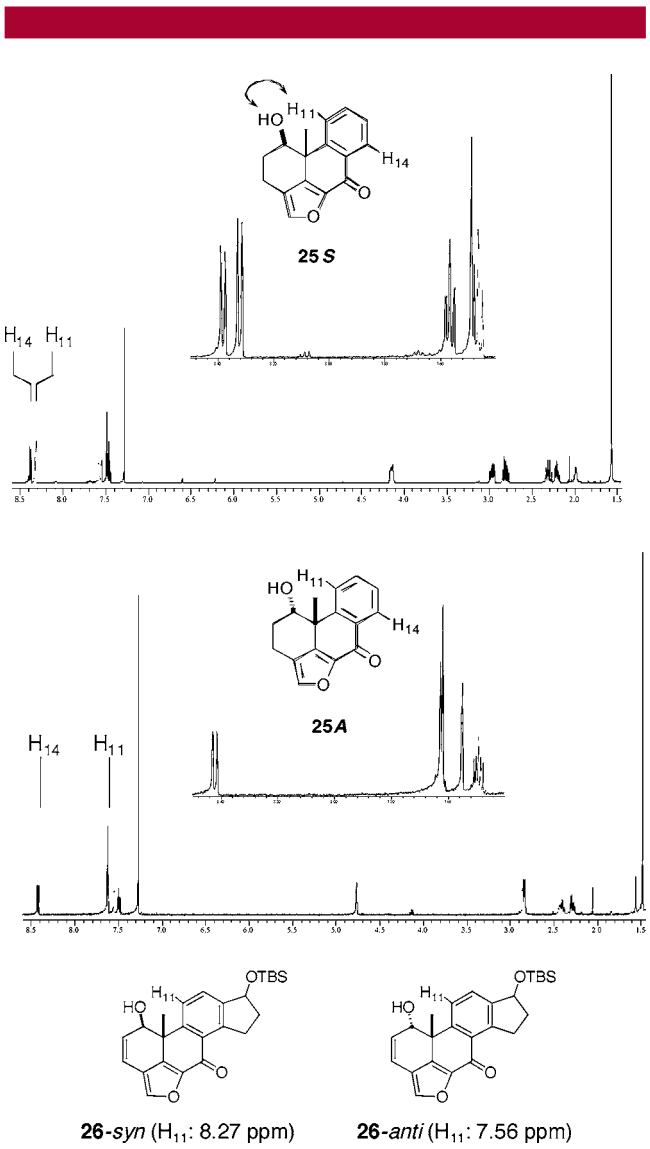

Figure 2. NMR spectra of viridin models **25**-*syn* and **25**-*anti*.

(8) The structures of **22** and **25*S***-*Ac* were confirmed by X-ray analysis. We are grateful to Mr. Benjamin E. Kucera and Dr. Victor G. Young, Jr., of the X-ray Crystallographic Laboratory of the University of Minnesota, Minneapolis, MN, for performing these analyses.

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(10) We are grateful to Mr. Erik Alexanian of Professor Sorensen's group for providing us with these spectra (compounds **16** and *epi*-**16** in ref 3m).