Intramolecular Diels−Alder and Cope Reactions of *o*-Quinonoid Monoketals and Their Adducts: Efficient Syntheses of (±)-Xestoquinone and Heterocycles Related to Viridin

Rina Carlini, Kerianne Higgs, Christina Older, and Sab Randhawa

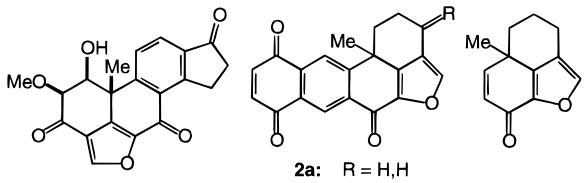
Guelph-Waterloo Center for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario N2L 3G1, Canada

Russell Rodrigo*

Department of Chemistry, Wilfrid Laurier University, Waterloo, Ontario N2L 3C5, Canada

Received March 4, 1997

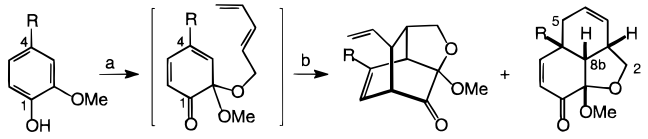
The viridin (**1**) family of steroidal antibiotics[1] as well as the xestoquinone (**2a**) and halenaquinone (**2b**) groups of marine natural products are pentacyclic compounds featuring a common naphtho[1,8-*bc*]furanone unit with an "angular" methyl group. Synthetic activity in this area has resulted[2] in many syntheses of **2a** and **2b**, but there have been no reports of any such success with the more challenging targets like viridin and its congeners, even though this group of antifungal agents have been known for much longer. The best synthesis[3] to date of a tricyclic naphthofuranone furnished **3** in 11 steps and 6.3% overall yield from α-furylmethanol. Although this work culminated in the synthesis of **2a** (1.5% overall, 14 steps), it was not efficient enough to be realistically regarded as a gateway to the viridin group of natural products. Our initial synthetic efforts[4] toward a tricycle like **3** were not successful, but their failure forced us to reexamine the problem and to look for a more direct route to this deceptively simple compound. Not only would success in this venture permit the development of a rapid synthesis of **2a** and **2b**, but it would also allow explorations to commence toward a first synthesis of viridin.



1 **3**

The formal similarity of the α-oxygenated cyclohexadienone moiety of **3** to *o*-benzoquinone prompted an investigation into the Diels−Alder chemistry of those highly reactive substrates. To ensure regiocontrol in the cycloaddition and to restrain the facile polymerization processes that plague the chemistry of simple *o*-benzoquinones, an intramolecular version of the reaction was considered. The test vehicles chosen for this purpose were mixed monoketals of *o*-quinones **5a**−**c** that could be easily generated *in situ* by oxidation of the respective

Scheme 1[a]



4a: R = Me	**5a**	**6a** (61%)	**7a** (8%)
4b: R = CO_2Me	**5b**	**6b** (44%)	**7b** (36%)
4c: R = COSMe	**5c**	**6c** (40%)	**7c** (37%)

[a] Conditions: (a) 1.2 equiv of $PhI[O_2CCF_3]_2$, 5 equiv of (*E*)-2,4-pentadienol, 2.4 equiv of $NaHCO_{3(s)}$, 2 mol % of BHT (for **4a**), dry THF, rt; (b) distill excess 2,4-pentadienol (bp = 58 °C/20 mmHg).

o-methoxyphenols **4a**−**c** in the presence of an excess amount of (*E*)-2,4-pentadienol (Scheme 1). The intramolecular Diels−Alder (IMDA) reaction that followed would compel the *o*-quinonoid monoketal to react as a diene[5] (to form **6**) and/or as a dienophile (to form **7**). The former pathway is predictably favored because of the *o*-quinonoid *s-cis* geometry, but we had hoped that the latter reaction, hitherto unprecedented, could be encouraged by the placement of electron-withdrawing substituents at C-4 of **4** to enhance dienophilicity of the *o*-quinonoid intermediate **5**. The results (Scheme 1) vindicated our thinking, but mixtures of **6** and **7** were always produced, and to tip the balance completely toward dienophilic reactivity, the unsubstituted double bond had to be removed from the game, and this could be done by making it part of an aromatic ring.

Thus, four substrates, three naphthalenoid **9a**−**c** and one anthracenoid **12a**, prepared from the corresponding *o*-methoxyphenols **8a**−**c** and **11a** provided good to excellent yields of the desired adducts **10a**−**c** and **13a** formed as *endo*−*exo*[6] mixtures (Scheme 2). All these reactions are "one-pot" three-step double annelation processes (oxidation, ketalization, and IMDA), and yields reported are for pure isolated materials. Furthermore, the same reaction with the tricyclic benzindanone substrate **15** produced **16** in 86% yield (2:1 *endo*−*exo*). Adduct **16** represents the first ever construction of the pentacyclic system of viridin and could be regarded as an advanced intermediate for the eventual synthesis of this compound. Although this new IMDA *dienophilic* reactivity of *o*-quinonoid species appeared to be general,[7] the reaction failed with **8d**; only red polymeric material was produced, probably through the formation of a *p*-quinomethide in the oxidation step. It is interesting but hardly surprising that the 9,10-dihydroanthraquinonoid ketal **12b** behaved like *o*-benzoquinonoid ketal **5c**, providing a mixture of **14** (32%) and the 7,12-dihydroderivative **13b** (23%, as the *endo* isomer only).

A reevaluation of the results of the IMDA reaction with the *o*-benzoquinonoid substrates **5** showed that the

(1) For a recent review see: Hanson, J. R. *Nat. Prod. Rep.* **1995**, *12*, 381−4.

(2) (a) Maddaford, S. P.; Anderson, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766−73 and references therein. (b) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1994**, *59*, 6606−13.

(3) Kanematsu, K.; Soejima, S.; Wang, G. *Tetrahedron Lett.* **1991**, *32*, 4761−4.

(4) Burns, P. A.; Taylor, N. J.; Rodrigo, R. *Can. J. Chem.* **1994**, *72*, 42−50.

(5) (a) Yamamura, S.; Shizuri, Y.; Shigemori, H.; Okuno, Y.; Okhubo, M. *Tetrahedron* **1991**, *47*, 635−644. (b) Chu, C.-S.; Lee, T.-H.; Liao, C.-C. *Synlett* **1994**, 635−6.

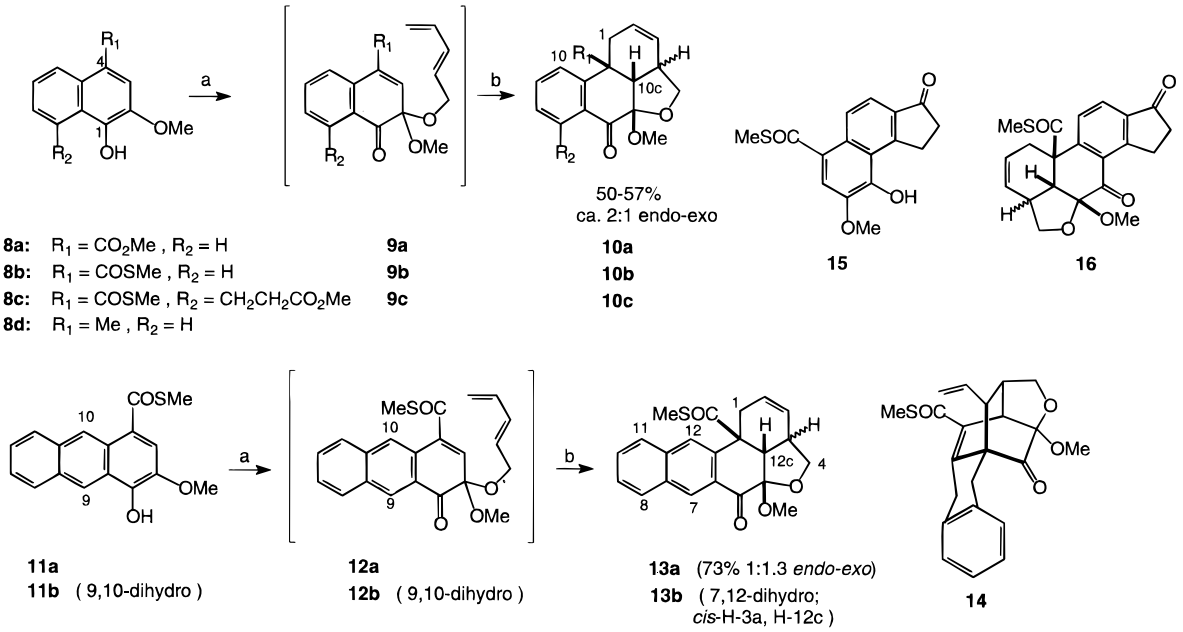
(6) All the IMDA reactions were face selective and *endo* with respect to the *o*-quinonoid ring.

(7) A 1,3-cyclohexadiene-5,6-diol carrying a pendant diene unit at the C-5 hydroxyl group produced only the bridged adduct in the IMDA reaction: Hudlicky, T.; Boros, C. H.; Boros, E. E. *Synthesis* **1992**, 174−6. We thank a reviewer for bringing this to our attention.

(8) X-ray crystal structures have been obtained for **10a** (*exo* and *endo*) and ^1H and ^{13}C NMR correlations made with the tricyclic moieties of the other adducts. An important diagnostic feature emerged when a small W-coupling of 2.2 Hz between H-1β and H-10c (established by decoupling and 2D correlation) was observed in the *endo* isomer of **10a**. This coupling is found in every other *endo* isomer of the tricyclic unit but is absent in every *exo* isomer.

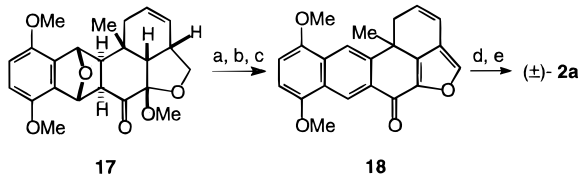
S0022-3263(97)00394-0 CCC: $14.00

Scheme 2[a]



[a] Conditions: (a) 1.2 equiv of $PhI[O_2CCF_3]_2$, 5 equiv of (*E*)-2,4-pentadienol, dry THF, rt; (b) distill excess 2,4-pentadienol (bp = 58 °C/20 mmHg).

Scheme 3[a]



[a] Conditions: (a) NaOMe/MeOH, reflux, 85%; (b) CF_3CO_2H, CH_2Cl_2, rt, 15 min, 90%; (c) *p*-chloranil, *p*-xylene, reflux, 87%; (d) H_2, Pd/C, EtOAc, 56%; (e) $Ce(NH_4)_2(NO_3)_6$, CH_3CN/H_2O, 63%.

tricyclic adducts **7** always possessed the *endo* stereochemistry[8] (*cis* H-2a, H-8b) in contrast to the *o*-naphthoquinonoid adducts, which were formed as mixtures (*ca.* 2:1 *endo*−*exo*). This apparent contradiction might be the consequence of the greater instability of the *o*-benzoquinonoid monoketals relative to the *o*-naphthoquinonoid substrates; reversal of the IMDA reaction may be energetically prohibitive[9] with adducts like **6** or **7**. Alternatively, the initially formed adducts **6** might have undergone spontaneous Cope rearrangements, which must only produce *endo* compounds. Such considerations persuaded us to attempt the [3,3]-shift by heating a pure sample of **6a** in refluxing 1,2,4-trimethylbenzene, and to our great satisfaction **7a** was produced in 81% yield with >95% conversion.

The acquisition of **7a** in two simple steps and 56% overall yield from 2-methoxy-4-methylphenol (**4a**) represents a significant improvement over the previous route[3] and constitutes an important bridgehead in our advance to the various pentacyclic natural products containing this structural unit.[1] We illustrate its value here with a rapid synthesis of (±)-xestoquinone (**2a**) (Scheme 3). Reaction with 4,7-dimethoxyisobenzofuran generated *in situ*[10] produced a single bridged adduct **17** (60%) by face-selective *exo* addition[11] to the enone **7a**. Aromatization, elimination of methanol, and dehydrogenation gave the known[2a] pentacycle **18** (66% from **17**). Hydrogenation of the alkene and oxidation of the *p*-dimethoxylated ring furnished (±)-xestoquinone (**2a**) in eight steps and 7.4% overall yield from 2-methoxy-4-methylphenol.[12]

The heartening success of this synthesis of **2a** encourages us to believe that the viridin and wortmannin[13] groups of biologically active metabolites are within relatively simple reach for the first time. Investigation of the road ahead to these complex natural products has already begun.

Acknowledgment. We thank NSERC Canada for support of this work and Dr. N. Taylor for X-ray crystal structures cited here.

Supporting Information Available: General experimental procedures are described for the intramolecular Diels−Alder (IMDA) reaction forming adducts **6a**−**c**, **7a**−**c**, **10a**−**c**, **13a**,**b**, **14**, and **16** and for the Cope rearrangement of **6a** to **7a**. Copies of ^1H NMR spectra are provided for compounds **6a**−**c**, **7a**−**c**, **10a**−**c** (endo and exo), **13a** (endo and exo), **13b**, **14**, **16** (endo and exo), and **17** (20 pages).

JO970394L

(9) It has been observed in our laboratory and in others that intermolecular Diels−Alder reactions of *o*-benzoquinones produce only the *endo*-adducts: Carlini, R.; Fang, C.-L.; Herrington, D.; Higgs, K.; Rodrigo, R.; Taylor, N. *Aust. J. Chem.* **1997**, in press.

(10) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093−2135 and references therein.

(11) An X-ray crystal structure of **17** established its relative stereochemistry. An adduct resulting from reaction of the isobenzofuran at the C2−C3 bond was also isolated (8%). See: Sadeghy, B. M. M.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 2237−46.

(12) All compounds were characterized by NMR and other common spectroscopic methods. Full details for the preparation of all previously unknown compounds will be published later.

(13) Hydrocortisone has recently been converted to wortmannin: Sata, S.; Nakada, M.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 6141−44.