nitrido ligand to a coordinatively unsaturated metal center (B). The critical difference between these two types of complexes is that the nitride bridges in **2-t** and **2-c** (A) are more robust than in complexes of type B. For example, whereas **3** dissociates to neutral $(Et_2PhP)_3Cl_2Re{\equiv}N$: and $[PtCl_2(PEt_3)]_2$ on attempted isolation,[17a] we do not observe dissociation of the μ_2-nitride bridge in **2** to produce an anionic terminal nitrido complex and a cationic metal center. This feature of the condensation reaction may prove important in synthesizing metallonitride polymers.

In summary, we have shown that a simple condensation reaction can be used to form a novel nitride-bridged vanadium-platinum derivative possessing robust metal nitrogen bonds. We are exploring the use of reaction 1 in the synthesis of not only bimetallic μ_2-nitride complexes but also transition-metal-containing nitride polymers.[7]

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Supplementary Material Available: Crystallographic data for **2-c**—ORTEP plot of all non-hydrogen atoms, crystal data, atomic coordinates, bond distances and angles, anisotropic temperature factors, and hydrogen atom coordinates (6 pages); observed and calculated structure factors for **2-c** (18 pages). Ordering information is given on any current masthead page.

A Stereoselective, Palladium-Catalyzed Route to 4-Oxygenated 5-Alkylidenecyclopentenones and 3-Oxygenated 2-Alkylideneindanones

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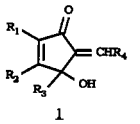
Eicosanoid derived marine natural products containing a 4-oxygenated 5-alkylidenecyclopentenone core **1**, such as the cla-



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vulones[2] (claviridenones[3]) chloro,[4] bromo-, and iodovulones,[5] and the punaglandins,[6] have been reported to possess remarkable cytotoxicity in both in vitro and in vivo studies.[7] In fact, non-naturally occurring arylidene cyclopentenediones also show significant in vitro antitumor activity.[8] The synthesis of 4-oxygenated 5-alkylidenecyclopentenones has been explored by numerous workers, although the stereoselectivity of the alkylidene formation has been rarely addressed.[9] We wish to describe a new, highly stereoselective, palladium-catalyzed reaction that provides rapid access to highly functionalized 4-oxygenated 5-alkylidenecyclopentenones and to 3-oxygenated 2-alkylideneindanones. The reaction holds promise for the synthesis of the naturally occurring eicosanoids mentioned above as well as for the synthesis of simpler analogues of the natural products.

Alkynyl anions add in high yield to cyclobutenediones[10] and benzocyclobutenediones[11] to give 4-alkynyl-4-hydroxycyclobutenones and 2-alkynyl-2-hydroxybenzocyclobutenones, respectively, and the reaction occurs with good regioselectivity with a number of unsymmetrically substituted substrates.[12] Excellent literature precedent[13] suggested that the 4-alkynyl-4-hydroxy-

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(10) Many cyclobutenediones can be prepared in large quantity from squaric acid by simple procedures. This chemistry will be described shortly.

(11) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3815-3821. Improved procedures will be described shortly.

(12) For some previous examples of this reaction, see: (a) Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3067-3068. (b) Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 1174-1175. (c) Karlsson, K. J. O.; Nguyen, N. V.; Foland, L. D.; Moore, H. W. *J. Am. Chem. Soc.* **1985**, *107*, 3392.

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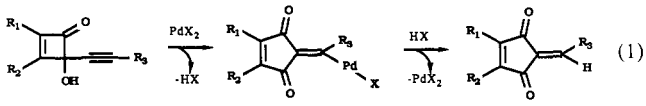
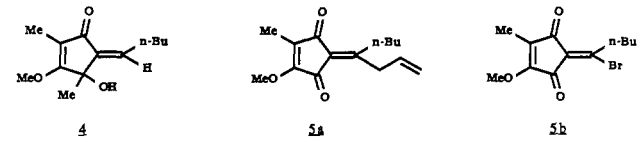
cyclobutenone ring system, **2**, might react with an electrophilic source of Pd(II) to effect ring expansion to an alkylidenecyclopentenedione possessing a vinyl–palladium bond.[14] As shown in equ 1, protonation of the vinyl–palladium bond by the HX gen-



(1)

erated in the ring expansion step would provide access to synthetically useful alkylidenecyclopentenediones **3** and regenerate the source of electrophilic Pd(II) rendering the reaction catalytic in Pd. This reaction proceeded as anticipated: when 4-(1-hexynyl)-4-hydroxy-3-methoxy-2-methyl-cyclobut-2-enone (**2a**) was treated with 10 mol % $Pd(OCOCF_3)_2$ in THF at 60 °C for 1 h, (*E*)-alkylidene cyclopentenedione **3a** was isolated together with the *Z*-stereoisomer in a 12:1 ratio in 45% yield.[15] Two other 4-alkynyl-4-hydroxycyclobutenones reacted similarly {10% $Pd(OCOCF_3)_2$ in THF at 40 °C for 5 h}: **2b** (R_1 = Me, R_2 = OMe, R_3 = Ph) gave 40% **3b** (15:1 ratio), and **2c** (R_1 = Me, R_2 = OMe, R_3 = $SiMe_3$) gave 49% **3c** (11:1 ratio). Confirmation of structure **3** as the major stereoisomer was achieved by reaction of **3a** with MeLi to give **4** in 80% yield. Since addition of MeLi to the more reactive ketone was anticipated, the observation of ^1H NMR vinyl hydrogen absorptions at δ 6.06 for the major isomer and δ 6.45 for the minor isomer dictate assignment of the stereochemistry in **4** to the stereoisomer with the higher field vinyl hydrogen absorption.

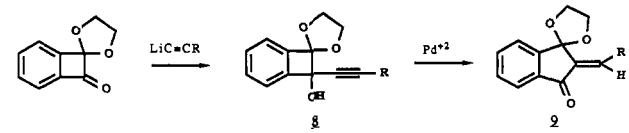
The intentional addition of acid to the reaction shown in eq 1 did not increase the yield of **3**, but we discovered that efficient trapping of the vinyl palladium intermediate could be effected by inhibiting the protonation with an acid scavenger (propylene oxide) and running the ring expansion reaction with 5% $Pd(OCOCF_3)_2$ at room temperature in CH_2Cl_2 in the presence of allyl bromide or NBS to provide the tetrasubstituted alkylidenecyclopentenediones **5a** and **5b**. In the former case a 73% yield



of the tetrasubstituted alkylidenecyclopentenedione **5a** was produced with a stereoisomer ratio of >20:1, while NBS efficiently gave the vinyl bromide **5b** as a 13:1 mixture of stereoisomers in 77% yield. Assignment of stereochemistry to **5a** and **5b** is presumed to follow that deduced for the protonated analogue **3**.

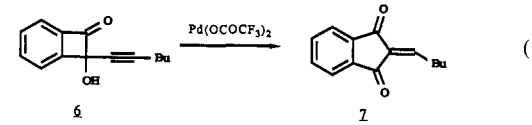
Extention of the ring expansion methodology to the 2-alkylideneindane-1,3-dione system was explored. Benzocyclobutenedione reacted with 1-lithiohexyne to give 2-(1-hexynyl)-2-hydroxybenzocyclobutenone (**6**) in 83% yield. Treatment of

Table I. Palladium-Catalyzed Formation of (*Z*)-2-Alkylideneindane-1,3-dione Monoketals



entry	R	yield (%), **8**	condtns[a] (%, h)	yield (%), **9**	isomer ratio
1	n-C_4H_9	92	2.5 $Pd(OTf)_2$, 12	91	36:1
2	n-C_6H_{13}	81	2.5 $Pd(OTf)_2$, 24	51	26:1
3	c-C_6H_{11}	97	2.5 $Pd(OTf)_2$, 10	75	>25:1
4	$SiMe_3$	84	2.5 $Pd(OTf)_2$, 12	56	20:1
5	Ph	92	2.5 $Pd(OTf)_2$, 12	89	20:1
6	CH_2OCH_3	90	2.5 $Pd(OTf)_2$, 12	84	>25:1
7	$CH(OTBDMS)CH_3$	97	5.0 $Pd(OTf)_2$, 10	66	18:1
8	$(CH_2)_2OTBDMS$	74	5.0 $Pd(OTf)_2$, 12	75	22:1

[a] All reactions were conducted at room temperature in CH_2Cl_2.

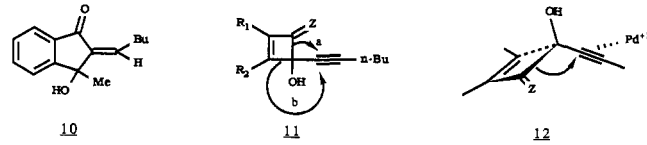


(2)

6 with 5% $Pd(OCOCF_3)_2$ in CH_2Cl_2 for 5h at room temperature gave 2-(1-pentylidene)indane-1,3-dione, **7**, in very good yield as judged from the ^1H NMR and IR spectra of the crude product; however, rapid decomposition occurred when purification was attempted on SiO_2 or other media (eq 2). To circumvent the reactivity of the 2-alkylidene indanediones, we explored the use of the alkynyl adducts of the ethylene glycol monoketal of benzocyclobutenedione[16] (83% yield from benzocyclobutenone) and carried through the sequence shown in Table I.

Significantly, the ketal-protected benzocyclobutenone derivatives 8 rearranged in excellent yield and stereoselectivity at room temperature (8–24 h) in the presence of 2.5–5.0% $Pd(OCOCF_3)_2$ to give the monoketal derivatives of 2-alkylidene indane-1,3-diones, **9**. In contrast to the highly sensitive 2-pentylideneindane-1,3-dione **7**, the monoketal derivatives were easily isolated, stable compounds. Again, as with the other ring expansions shown above, the transformations of the benzocyclobutene derived ring systems occurred with high stereoselectivity, and the chemical shift of the olefinic hydrogens observed for both isomers was used to establish the stereochemistry of the predominant regioisomer.

On rearrangement, products **9** are provided with carbonyl groups suitably differentiated for chemoselective transformation. Clean 1,2-addition of carbon nucleophiles, a reaction not possible with use of Grignard or lithium reagents, was achieved through the use of the organocerium derivatives.[17] Thus, the 1,2-addition of $MeCeI_2$ (THF, −78 °C, 10 min) followed by a mild acid hydrolysis provided a very efficient method for the synthesis of **10** (85%), a benzo analogue of the biologically active 4-oxygenated 5-alkylidenecyclopentenone ring system, **1**.



Z = =O or ketal

How do we rationalize the exceptional stereoselectivity observed in the palladium-induced ring expansions of 4-alkynyl-4-hydroxycyclobutenones and 2-alkynyl-2-hydroxy benzocyclobutenones? Two factors seem to be operating to influence the stereochemical outcome of these reactions. First, it is apparent that only one of two possible bonds, a or b in **11**, is migrating to

(13) Clark, G. R.; Thiensathit, S. *Tetrahedron Lett.* **1985**, 2503–2506. Treatment of 1-hydroxy-1-vinylcyclobutanes with stoichiometric Pd(II) effected a ring expansion to cyclopentenones. In this chemistry, ring expansion generates an alkyl palladium that decomposes by β-hydride elimination to form an alkylidene cyclopentanone that is isomerized to the cyclopentenone by the palladium hydride generated in β-hydride elimination step. For a related four- to five-membered ring expansion, see: Boontanonda, P.; Grigg, R. *J. Chem. Soc., Chem. Commun.* **1977**, 583–584.

(14) Palladium induced ring expansion of **2** could have occurred to form the proposed 5-alkylidenecyclopent-2-ene-1,4-dione or a 5-alkylidenecyclopent-3-ene-1,2-dione. The latter ring system appears to be unknown, so we cannot rely on established spectroscopic differences to verify structure **3** as the product. However, we have prepared and rigorously characterized a number of 5-alkylidenecyclopent-2-ene-1,4-diones by the chemistry described by Liebeskind and Chidambaram (Liebeskind, L. S.; Chidambaram, R. *J. Am. Chem. Soc.* **1987**, *109*, 5025–5026), and the spectroscopic data obtained for the products of the palladium-catalyzed reaction are in complete accord with the structures proposed. Spectroscopic arguments were used to deduce the structures of the products formed in the other palladium induced ring expansions described in the paper. Concerted 1,2-carbonyl migrations are precedented: Bach, R. D.; Domagala, J. M. *J. Chem. Soc., Chem. Commun.* **1984**, 1472–1474. Bach, R. D.; Klix, R. C. *Tetrahedron Lett.* **1985**, *26*, 985–988.

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the adjacent sp hybridized carbon. Ring expansions from four- to five-membered rings are very common, and a number of rationalizations for the selectivity of the ring expansions have been advanced.[18] In our examples, it appears that the non-vinyl or non-aryl carbon, a in **11**, selectively migrates in every case.[14] While the ability of the migrating group to stabilize positive charge probably plays some role in governing the selectivity of the reaction, we can explain the outcome of the ring expansion by postulating a reaction path that proceeds through the best stabilized cationic intermediate. Then, formation of the final product is concluded in a stereospecific fashion by trans addition across the alkyne bond as depicted in **12**.

Acknowledgment. This investigation was supported by PHS Grant No. CA 44404 awarded by the National Cancer Institute, DHHS.

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About the Mechanism of Sterol Biosynthesis

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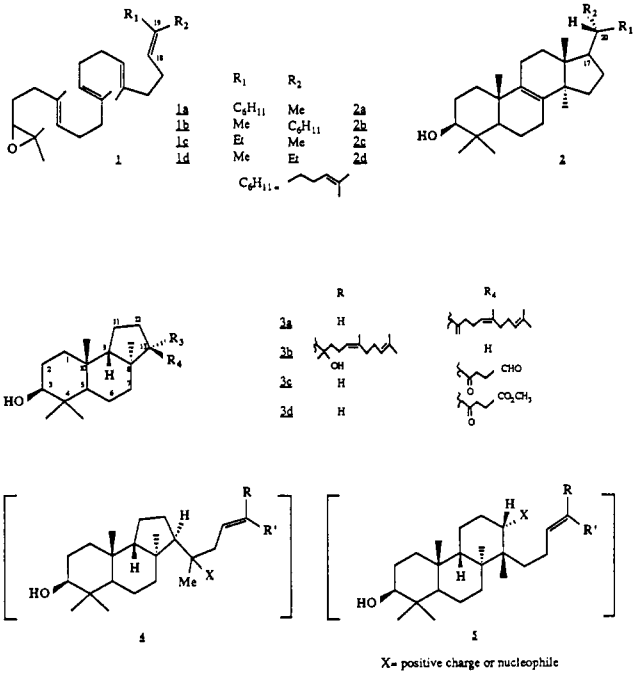
The transformation of 2,3-oxido-(*all trans*)-squalene **1a** to lanosterol **2a** possessing not less than seven asymmetric centers has been the subject of intensive work since the first hypothesis of Woodward and Bloch and the brilliant theoretical models proposed[1] independently by the Zurich School and by Stork.

Although several aspects of these hypotheses have been supported by careful experiments with radiolabeled 2,3-oxidosqualene or with analogous lacking one or several methyl groups,[1] the problems related to the C-20 carbon atom of lonosterol have not yet been clarified. It is well established however that the cyclization process ends at this position and also that a 120° rotation of the alkyl chain around the C-17-C-20 bond must precede the series of migrations in order to achieve the 20 (*R*) stereochemistry found in lanosterol.[1]

In a previous study we found[2] that the truncated 2,3-oxidosqualene analogues **1c** and **1d** possessing $\Delta^{18\text{-}19}$ double bonds with the natural *E* and the unnatural *Z* stereochemistry produce the tetranorlanosterols **2c** and **2d**, respectively, having the natural 20 (*R*) and the unnatural 20 (*S*) stereochemistry. As a continuation of this work it became particularly important to study the behavior of the 2,3-oxidosqualene **1b** with the complete hydrocarbon framework but with the unnatural *Z* stereochemistry at $\Delta^{18\text{-}19}$. This compound possessing a tritium radiolabel at C-3 has been prepared from the commercially available pure *all-trans*-farnesol (**3a**) as the basic subunit by using the well-established Biellman method[3] for the construction of the complete skeleton possessing the correct oxidation level at C-2 and at C-3 and a *Z* $\Delta^{18\text{-}19}$ carbon-carbon double bond. We have adopted as the key step an unusual strategy purposely implying a nonregioselective oxidation of the *trans,trans*-farnesol in order to achieve *in one step* the differentiation between the two different subunits required.[4]



Anaerobic incubation of the racemic labeled oxide **1b** (250 μg, 4.14×10^{-6} dpm) at 20 °C with a solution (6 mL) of oxidosqualene sterol cyclase[5] affords a mixture of compounds containing 92% of the initial radioactivity, which exhibits on thin-layer radiochromatography on SiO_2 (eluted with benzene/ethyl acetate, 9/1) four major radioactive spots: (i) a fraction A which corresponds to the unchanged labeled oxide (59%, R_f 0.84), (ii) a fraction B (6%, R_f 0.50), (iii) a fraction C (16%) whose R_f (0.43) is close to that of lanosterol (R_f 0.44), and (iv) a more polar fraction D (19%, R_f 0.29).

On silver nitrate impregnated SiO_2 TLC (eluted with benzene/ethyl acetate, 8:2), fraction B (R_f 0.34), fraction C (R_f 0.52), and fraction D (R_f 0.20) are all more polar than lanosterol or its iso 20 (*S*) stereoisomer[6] (R_f 0.70). The complete absence of the latter two compounds in our biosynthetic mixture was further unambiguously confirmed by |GC|[2] and HPLC experiments which include co-injection with authentic samples.[6] It is therefore clear that this biosynthesis takes a different course from that of 2,3-oxido-(*all trans*)-squalene (**1a**) or from that of 2,3-oxidotetranorsqualene (**1d**) possessing the $\Delta^{18\text{-}19}$ *Z* stereochemistry.

Fractions B, C, and D contain several exogeneous products, but each fraction presents a major radiolabeled derivative. These compounds have been separated by HPLC (column Varian RP 18, 50 × 1 cm, eluted with acetonitrile, flow rate 5 mL/min, UV detector 200 nm, *D* (Rt 20 mn), *B* (Rt 24 mn) and *C* (Rt 33 mn)). After several large scale experiments and purification of the crude mixtures on PLC then on HPLC according to the previously

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(1) For a review article, see: Mulheirn, L. J.; Ramm, P. J. *Chem. Soc. Rev.* **1972**, 259.

(2) Herin, M.; Delbar, P.; Remion, J.; Sandra, P.; Krief, A. *Tetrahedron Lett.* **1979**, 1073.

(3) Biellman, J. F.; Ducep, J. B. *Tetrahedron* **1971**, *27*, 5861.

(4) The details of this synthesis will be reported later.

(5) (a) Hogebomm, S. H. *Methods in Enzymology*; Colowich, S. P., Kaplan, N. O., Eds.; Academic Press: 1955; Vol. 1, p 16. (b) A phosphate-buffered microsomal solution (70 mL) was prepared in the standard manner[5a] from minced hog liver (700 g) without any further purification. We are indebt to S. Wattiaux (Medical Faculty, Namur) for her help for the preparation of the microsomal solution. (c) **1b** remains unchanged if the enzymic solution is boiled for 0.3 h prior incubation.

(6) Schauder, J. R.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 4389.

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