and the reaction was allowed to proceed for another 3 h. Analysis of the reaction mixture at this point indicated only 69% ketone. Octanoic acid exerted a comparable inhibition when added to 2-octanol at the outset. Although these results show that a selective oxidation is unfeasible, they also illustrate the intricacies of organic reactions on solid surfaces and the need for future research in the area.

Acknowledgment. This work was supported by the National Science Foundation and the National Institutes of Health.

Registry No. 2-Octanol, 123-96-6; 2-hexadecanol, 14852-31-4; benzhydrol, 91-01-0; 1-cyclohexylethanol, 1193-81-3; 3-methylcyclohexanol, 591-23-1; ethyl lactate, 97-64-3; cholestanol, 80-97-7; 1-octanol, 111-87-5; 2-octanone, 111-13-7; 2-hexadecanone, 18787-63-8; diphenyl ketone, 119-61-9; 1-cyclohexylethanone, 823-76-7; 3-methylcyclohexanone, 591-24-2; ethyl 2-oxopropanoate, 617-35-6; cholestan-3-one, 566-88-1; octanal, 124-13-0; $KMnO_4$, 7722-64-7; $CuSO_4$, 7758-99-8.

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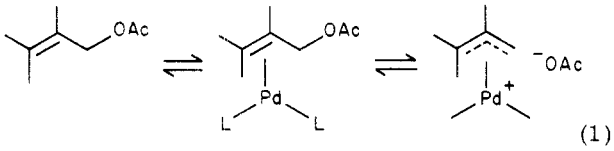
An Approach to Enolonium Equivalents. Application to a Total Synthesis of (±)-Pyrenophorin

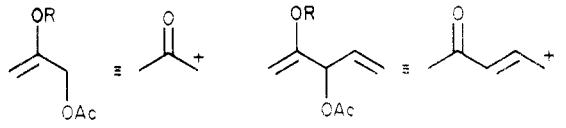
Summary: Alkoxy-bearing allylic acetates can serve as substrates for palladium(0) catalysts under special conditions and thus constitute the equivalent of an enolonium and a vinylogous enolonium ion, a feature that has led to a formal synthesis of pyrenophorin and a synthesis of a fragment of zealeranone.

Sir: Allylic alkylations catalyzed by palladium(0) complexes have proven quite versatile for structural elaboration.[1,2] Activation of allylic acetates by a palladium complex involves initial coordination to form an olefin–metal(0) complex followed by ionization of the acetate (eq 1). Allylic acetates that fail to react frequently do so



(1)

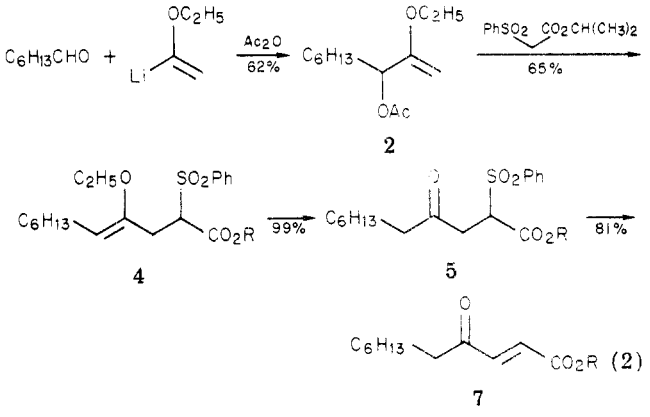
presumably because of the unfavorability of formation of the initial olefin complex. Whereas electron-withdrawing substituents facilitate the formation of such complexes, electron-donating ones greatly hamper it.[3] On the other hand, allylic acetates bearing an electron-donating group like a heteroatom should be particularly useful as carbonyl equivalents; for example, **1a** would be an equivalent of an



1a **1b**

enolonium ion[4] and **1b** an equivalent of a vinylogous enolonium ion. In this communication, we wish to report that, while the usual procedures for alkylation of allylic acetates like **1** fail, we have uncovered a successful set of conditions for alkylation. Furthermore, use of such systems evolved the equivalent of a reductive acylation, a stereocontrolled enol ether synthesis, and the synthesis of oxygen-bearing dienes. The reductive acylation is applied to the synthesis of the antifungal and cytostatic agent pyrenophorin[5] and a segment of the commercial anabolic agent zealeranone.[6]

The requisite substrates are readily available by the addition of lithiated ethyl vinyl ether[7] to aldehydes (THF, −78 °C) followed by acetylation (C_5H_5N, Ac_2O, room temperature) as in eq 2. For synthetic purposes, our



interest focused upon the anions from sulfonylacetates. Treatment of **2** with methyl benzenesulfonylsodioacetate in THF in the presence of tetrakis(triphenylphosphine)palladium (**3**) led to mostly decomposition. On the other hand, reaction with isopropyl benzenesulfonylacetate[8] and DBU in hot toluene in the presence of 10–15 mol % of **3** proceeded smoothly to give a single product, **4**.[9] It is interesting to note that higher regioselectivity is observed here compared to allylic acetates without the heteroatom substituent and that a single stereoisomeric enol ether is formed as shown by chromatography and spectral analysis including ^{13}C NMR spectroscopy. The appearance of the vinyl carbons at δ 115.5 and 148.4 suggest the *Z* configuration,[10] in agreement with reaction via the expected syn palladium complex. Hydrolysis of **4** (0.02 N HCl in THF, room temperature) unmasks the carbonyl group to give **5**.[9] In principle, desulfonylation[11]

(1) For reviews, see: Trost, B. M. *Tetrahedron* **1977**, *33*, 2615; *Pure Appl. Chem.* **1979**, *51*, 787.
(2) For most recent work see: Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864. Trost, B. M.; Verhoeven, T. R. *Ibid.*, **1978**, *100*, 3435. Trost, B. M.; Godleski, S.; Genet, J. P. *Ibid.* **1978**, *100*, 3930. Trost, B. M.; Verhoeven, T. R. *Tetrahedron Lett.* **1978**, 2275. Trost, B. M.; Keinan, E. *J. Am. Chem. Soc.* **1978**, *100*, 7779. Trost, B. M. Verhoeven, T. R. *Ibid.* **1979**, *101*, 1595. Trost, B. M.; Godleski, S.; Belletire, J. *J. Org. Chem.*, **1979**, *44*, 2052.
(3) Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *J. Organomet. Chem.* **1979**, 168, 375. Itoh, K.; Ueda, F.; Hirai, K.; Ishii, Y. *Chem. Lett.* **1977**, 877. Visser, A.; van der Linde, R.; de Jongh, R. J. *Inorg. Synth.* **1976**, *16*, 127. Tolman, C. A.; Seidel, W. C.; Gerlach, D. H. *J. Am. Chem. Soc.* **1972**, *94*, 2669. Roundhill, D. M.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 506.
(4) For some alternative enolonium equivalents, see: Miyashita, M.; Yanami, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4679, and references cited therein. Sacks, C. E.; Fuchs, P. L. *Ibid.* **1975**, *97*, 7372. Fuchs, P. L. *J. Org. Chem.* **1976**, *41*, 2935. Stork, G.; Ponaras, A. A. *Ibid.* **1976**, *41*, 2937. Herrmann, J. L.; Kieczykowski, G. R.; Romanet, R. F.; Wepplo, P. J.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 4711.
(5) Nozoe, S.; Hirai, K.; Tsuda, K.; Ishibashi, K.; Shirasaka, M.; Gove, J. F. *Tetrahedron Lett.* **1965**, 4675. Grove, J. F. *J. Chem. Soc. C* **1971**, 2261.
(6) For a review see: Shipchandler, M. T. *Heterocycles* **1975**, *3*, 471.
(7) Schöllkopf, U.; Hänssle, P. *Ann. Justus Liebigs Chem.* **1972**, *763*, 208. Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.
(8) The use of DBU as base precluded employing methyl benzenesulfonylacetate since decarbomethoxylation accompanied alkylation: cf. Miles, D. H.; Huang, B. S. *J. Org. Chem.* **1976**, *41*, 208.
(9) New compounds have been fully characterized by spectral means and elemental composition.
(10) Taskinen, E. *Tetrahedron* **1978**, *34*, 425.

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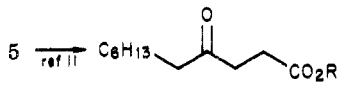
of **5** to **6** would constitute a net reductive succinoylation

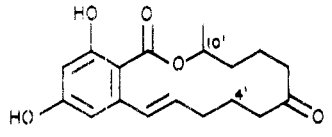


6

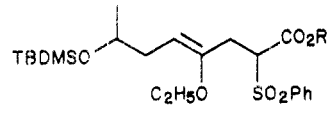
of a carbonyl group.[12] Of greater synthetic interest to us, mild base treatment ($(C_2H_5)_3N$, THF, room temperature) gave **7**[9] (δ 6.6 and 7.1, J = 17 Hz), the product of reductive fumaroylation.

Such a reductive fumaroylation allows a strategy for the synthesis[13] of pyrenophorin **13** to begin with aldol **8** as outlined in Scheme I. The key alkylation reaction proceeded as in the model to give **10a**[9] regioselectively. While the isopropyl ester was taken through the sequence to **12**,[9] in order to merge with the Gerlach intermediate **12b**,[13c] **10a** was transesterified to the methyl ester **10b**[9] and taken on as outlined via **11b**[9] [δ 1.20 (13 H, d, J = 6 Hz), 2.78 (2 H, t, J = 7 Hz), 3.71 (1 H, m), 6.65 (1 H, d, J = 16 Hz), 7.10 (1 H, d, J = 16 Hz)] to give **12b**.[9] Since Gerlach[13c] had converted **12b** to pyrenophorin (**13**), this route constitutes a formal synthesis of this macrodiolide.

In a proposed synthesis of zealeranone (**14**), a unit

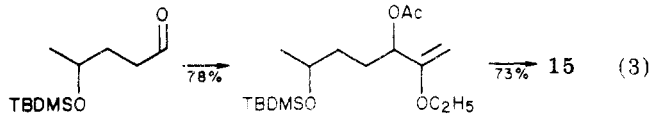


14



15

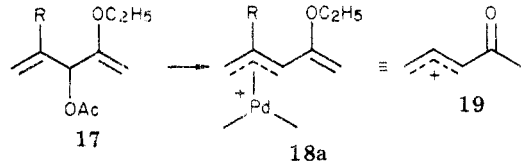
representing C(4′)–C(10′) was projected to be **15**. As outlined in eq 3, **15**[9] is readily available in 57% overall yield from the homologue of the protected aldol, **16**, by a sequence identical to that employed in Scheme I.



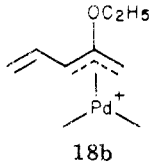
(3)

16

The equivalent of a vinylogous enolium ion **19** is



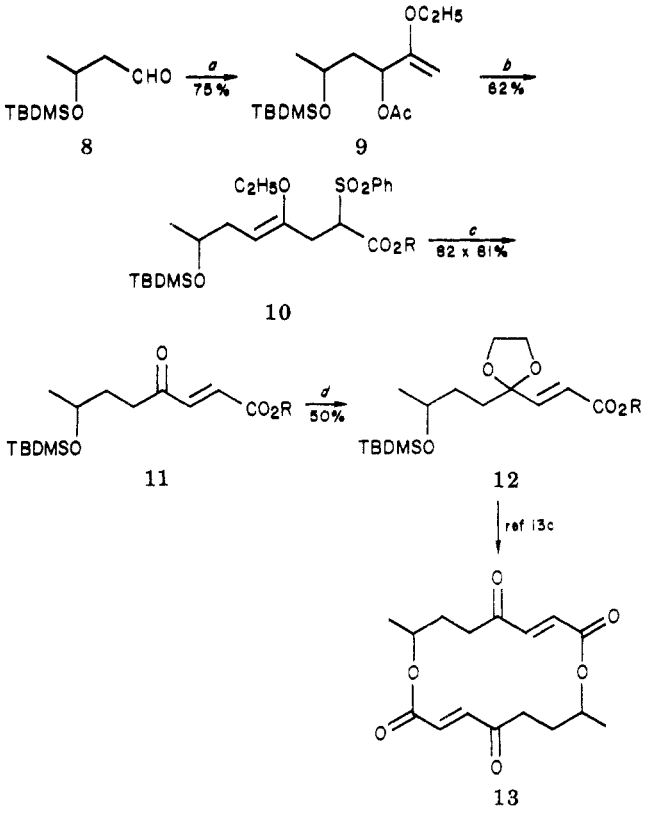
17 **18a**



18b

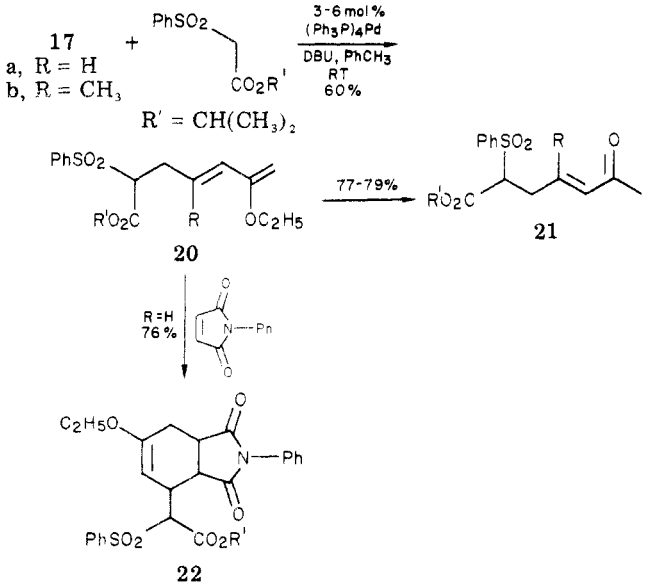
available from substrates such as **17**, which arise by addition of lithiated ethyl vinyl ether to α,β-unsaturated aldehydes. This substrate also tests the chemoselectivity, competing **18a** with **18b**. The deactivating influence of the ethoxy group was readily apparent by the fact that **17** underwent exclusive reaction via **18a** to give **20**[9] and the

Scheme I. Synthesis of Pyrenophorin (13)



a, R = $CH(CH_3)_2$
b, R = CH_3
TBDMS = $(CH_3)_3CSi(CH_3)_2$-

[a] (i) CH_2=C(Li)OC_2H_5, THF, −78 °C. (ii) Ac_2O, C_5H_5N, room temp. [b] (i) $PhSO_2CH_2CO_2C_3H_7$-*i*, DBU, 13 mol % $(Ph_3P)_4Pd$, $PhCH_3$, 80 °C. (ii) $NaOCH_3$, CH_3OH, reflux. [c] (i) camphorsulfonic acid, $(CH_3)_2CO$, room temp. (ii) $(C_2H_5)_3N$, CH_2Cl_2, room temp. [d] $HOCH_2CH_2OH$, camphorsulfonic acid, PhH, reflux.



22

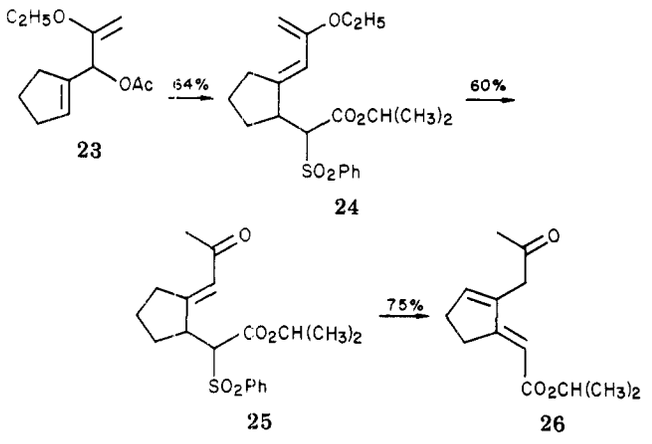
reaction proceeded at room temperature. While **20a** was homogeneous (^{13}C NMR δ 85.25, 121.68, 129.02, 155.9) and

(11) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

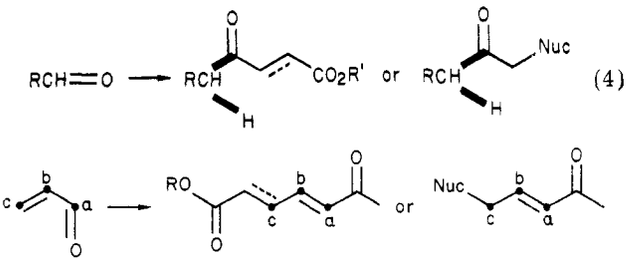
(12) Cf. Nakamura, E.; Hashimoto, K.; Kuwajima, I. *J. Org. Chem.* **1977**, *42*, 4166.

(13) For prior syntheses see: (a) Colvin, E. W.; Purcell, T. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1718. (b) Seebach, D.; Seuring, B.; Kalinowski, H.; Lubosch, W.; Renger, B. *Angew Chem., Int. Ed. Engl.* **1977**, *16*, 264. (c) Gerlach, H.; Oertle, K.; Thalmann, A., *Helv. Chim. Acta*, **1977**, *60*, 2860. (d) Bakuzis, P.; Baukzis, M. L. F.; Weingartner, T. F. *Tetrahedron Lett.* **1978**, 2371. (e) Seebach, D.; Pohmakotr, M. *Helv. Chim. Acta* **1979**, *62*, 843.

gave **21a**[9] upon hydrolysis (1 M H_2SO_4, THF) identified as the *E* isomer (δ 6.18 and 6.7, J = 18 Hz), **20b**[9] appears to be a mixture of olefin stereoisomers which upon hydrolysis gave a 3:2 mixture of geometric isomers of **21b** [δ 6.19 (0.67 H), δ 6.3 (0.33 H)]. The use of such dienes as **20** in cycloaddition was illustrated by the reaction with *N*-phenylmaleimide in $CHCl_3$ at room temperature to **22**,[9] mp 145–148 °C. Additional alkyl substitution as in **23**[9] still leads to reaction via the non-oxygen-bearing olefin to give **24**[9] (64%), which after hydrolysis and elimination gave **26**,[9] a product of base-catalyzed isomerization of the initial diene.



While oxygen-bearing allylic acetates are sluggish substrates for palladium(0), they do participate in allylic alkylations. As a result of the substitution pattern of the allylic acetates and the nucleophile employed here, novel strategy emerges as summarized in eq 4 and 5. By use of other nucleophiles, these "reductive acylations" can provide even broader applicability. It should also be noted that this reaction represents one of the few ways to make stereodefined enol ethers.[14]



Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. F.G. thanks the National Research Council of Canada for a postdoctoral fellowship. We appreciate the generosity of Englehardt Industries and Mathey Bishop for supplies of palladium chloride.

Registry No. (±)-**2**, 71171-63-6; (±)-4 (R = $CH(CH_3)_2$), 71194-25-7; (±)-**5** (R = $CH(CH_3)_2$), 71171-64-7; **7** (R = $CH(CH_3)_2$), 71171-65-8; (±)-**8**, 71171-66-9; **10a**, 71171-67-0; **10b**, 71171-68-1; (±)-**11b**, 71171-69-2; (±)-**12a**, 71171-79-4; (±)-**12b**, 71171-70-5; (±)-**13**, 38634-44-5; **15** (R = $CH(CH_3)_2$), 71171-71-6; (±)-**16**, 71171-72-7; (±)-**17a**, 71171-73-8; (±)-**17b**, 71171-74-9; (±)-**23**, 71171-75-0; (±)-**24**, 71171-76-1; **26**, 71171-77-2; heptanal, 111-71-7; (1-ethoxyethenyl)lithium, 40207-59-8; isopropyl benzenesulfonylacetate, 71171-78-3; *N*-phenylmaleimide, 941-69-5.

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Received May 1, 1979

(14) Cf. Hudrlik, P. F.; Hudrlik, A. M.; Rona, R. J.; Misra, R. N.; Withers, G. P. *J. Am. Chem. Soc.* **1977**, *99*, 1993.