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SYNTHETIC STUDIES ON PARAHERQUAMIDE: SYNTHESIS OF THE 2H-1,5-BENZODIOXEPIN RING SYSTEM

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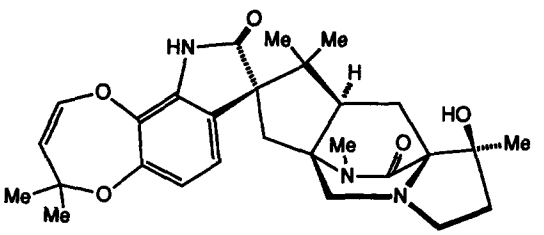
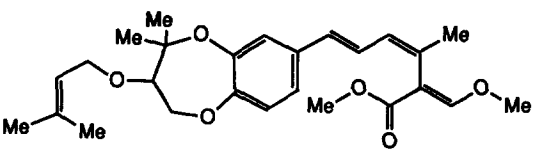
Summary: *Various 2H-2,2-dimethyl-1,5-benzodioxepins have been synthesized en route to the oxindole moiety of paraherquamide (1). The key step is the 7-membered ring formation from prenylated catechols using either PhSeCl, N-PSP or m-CPBA/$SnCl_4$.*

Paraherquamide (1) is a mycotoxic alkaloid isolated from the mold *Penicillium paraherquei.*[1] Lately, there has been an increase of interest surrounding this molecule since the discovery by a Merck group that it has anti-parasitic properties.[2] The relative configuration of this alkaloid was determined by a single crystal x-ray analysis;[1] additionally an x-ray analysis of a semi-synthetic degradation product established the absolute configuration.[3] As part of our efforts to effect the total synthesis of **1**, we recently reported a model study which embraces some of the problems inherent in controlling stereo- and regiochemical issues.[4] This paper describes the construction of the 1,5-dioxepin oxindole moiety of **1** and the related portion of the recently discovered antibiotic Strobilurin G (**2**).[5] Both substances represent the biosynthetic oxidative incorporation of dimethallyl pyrophosphate to a catechol.



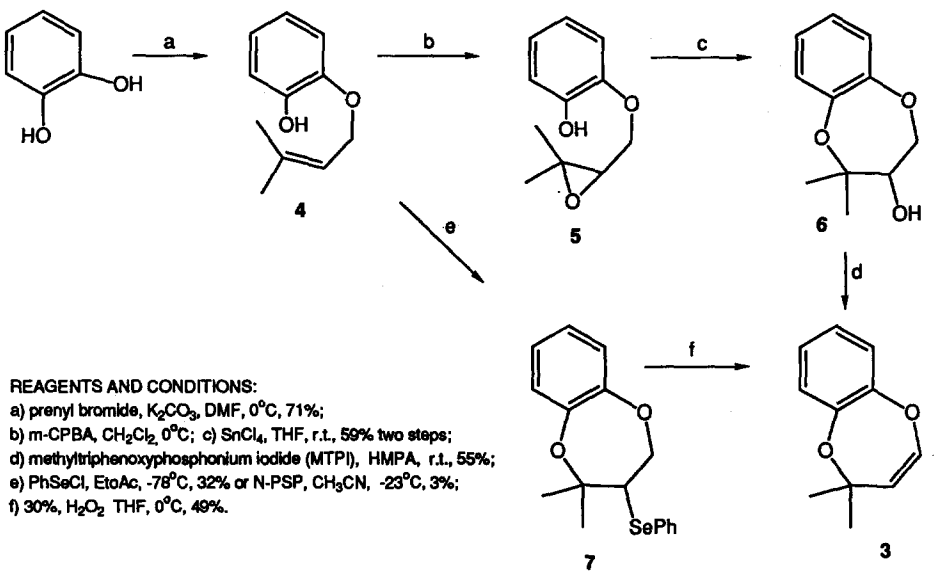
1, PARAHERQUAMIDE



2, STROBILURIN G

The 2H-1,5-benzodioxepin ring system has been named[6] although never synthesized; a thorough search of the literature uncovered no precedent for the 2H-2,2-dimethyl-1,5-benzodioxepin skeleton (**3**). The synthesis of this simple ring system was done *via* two distinct ring forming reactions. First, catechol was prenylated to give the phenol **4**. This was followed by epoxidation with m-CPBA to provide **5**. Ring closure by the method of Cookson/Kocieński,[7] and subsequent dehydration of the alcohol[8] gave **3**. Alternatively, the prenylated catechol **4** could be treated with PhSeCl[9] or N-phenylselenophthalimide (N-PSP),[11] followed by oxidation and then elimination of the resulting selenoxide to yield, **3** (Scheme 1). Since the key 7-membered ring-forming step proved amenable by both approaches, our attention turned to the construction of the oxindole moiety of **1**.

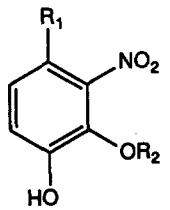
Scheme 1



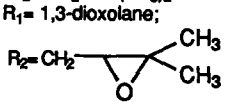
REAGENTS AND CONDITIONS:
a) prenyl bromide, K_2CO_3, DMF, 0°C, 71%;
b) m-CPBA, CH_2Cl_2, 0°C; c) $SnCl_4$, THF, r.t., 59% two steps;
d) methyltriphenoxyphosphonium iodide (MTPI), HMPA, r.t., 55%;
e) PhSeCl, EtoAc, -78°C, 32% or N-PSP, CH_3CN, -23°C, 3%;
f) 30%, H_2O_2 THF, 0°C, 49%.

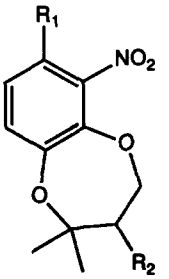
O-nitrovanillin [10] (**8**) is easily demethylated (BBr_3, CH_2Cl_2, -78°C, 92%) to give the catechol **9**. Prenylation of **9** (prenyl bromide, K_2CO_3, DMF, 0°C) furnishes **10** in 20% yield, together with its regio-isomer and the dialkylated compound. Treating **10** with N-PSP (CH_3CN, CSA cat. amount, -23°C) results in the formation of the seven-membered ring selenide **14** in 52% yield, which is smoothly converted (30%, H_2O_2, THF, 0°C, 68%) or (m-CPBA, THF, 0°C, 99%) to the dioxepin **18**. We expected that by masking the electron withdrawing aldehyde functionality in **9**, a higher yield of the correct prenylated compound could be obtained. The catechol **9** was protected (ethylene glycol, TsOH, benzene, reflux, 100%) as the cyclic acetal **11**, which was in turn prenylated (prenyl bromide, K_2CO_3, DMF, 0°C) to afford **12** in 71% yield. This compound could then be deblocked (5% HCl, THF, r.t., 99%) to furnish **10** or reacted further, (N-PSP, CH_3CN, CSA cat. amount, -23°C, 48%) rendering the acetal **16**. Selenide **16** was smoothly eliminated (m-CPBA, $NaHCO_3$, THF, 0°C, 87%) to yield the dioxepin **19**. In the parent system described above (Scheme 1) the best results were obtained with the Lewis-acid mediated ring closure procedure, while in this system the selenium assisted cyclization proved the most facile. The prenylated aldehyde **10** was found to be intractable toward epoxidation. The six-membered ring tertiary alcohol forms rapidly, together with an unidentified side product in the presence of m-CPBA. Interestingly, we had no trouble epoxidizing the acetal **12** (m-CPBA, $NaHCO_3$, 0°C, 100%) supplying **13** which was subjected to $SnCl_4$ (THF, r.t.) to give **17** in 31% yield. This compound is deprotected (5% HCl, THF, r.t., 74%, recrystallized) to provide **15**, which was eliminated (MTPI, HMPA, r.t., 43%) giving **18** (Scheme 2).

Scheme 2

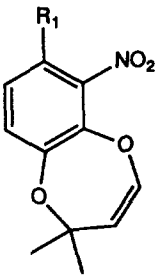


8) R_1 = CHO; R_2= CH_3
9) R_1= CHO; R_2= H
10) R_1= CHO; R_2= $CH_2CHC(CH_3)_2$
11) R_1= 1,3-dioxolane; R_2= H
12) R_1= 1,3-dioxolane; R_2= $CH_2CHC(CH_3)_2$
13) R_1= 1,3-dioxolane;





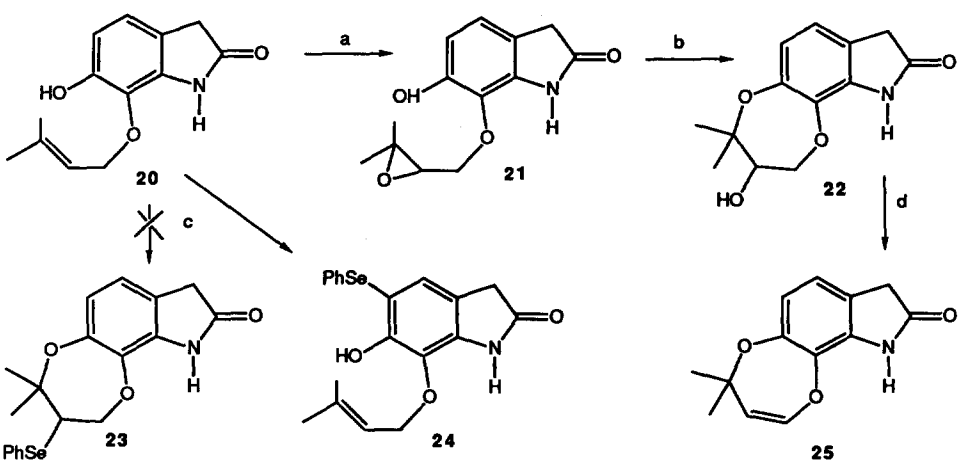
14) R_1= CHO; R_2= SePh
15) R_1= CHO; R_2= OH
16) R_1= 1,3-dioxolane; R_2= SePh
17) R_1= 1,3-dioxolane; R_2=OH



18) R_1= CHO
19) R_1= 1,3-dioxolane

An alternative route to the dioxepin oxindole ultimately proved to be more successful (Scheme 3). The prenylated oxindole **20** which was prepared in 8 steps from vanillin[12] was smoothly epoxidized to give **21**. This was followed by treatment with $SnCl_4$ to give the alcohol **22** which was subsequently eliminated to the dioxepin **25** in good overall yield. However in this sequence the phenylselenoetherification failed to form the ring closed product **23**; only compounds such as **24** were isolated under these conditions (Scheme 3).

Scheme 3



a) m-CPBA, $NaHCO_3$, 0°C, 100%; b) $SnCl_4$, THF, r.t., 70%; c) N-PSP , CH_2Cl_2 , -78°C or PhSeCl, EtoAc, -78°C; d) MTPI, HMPA, r.t.,58%.

In conclusion we have demonstrated two different approaches for the construction of the hitherto unknown 2H-2,2-dimethyl-1,5-benzodioxepin ring system with various substituents. The complete details of the synthesis of compound **25** and other analogs will be described subsequently.

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References and Footnotes

1. Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* (1981), **22**, 135.

2. (a) European Patent 301742A Merck and Co. (July 29, 1987). (b) Blizzard, T.A.; Mrozik, H.; Fisher, M.H.; Schaeffer, J.N. *J. Org. Chem.* (1990), **55**, 2256. (c) Ostland, D.A.; Mickle, W.G.; Ewanciw, D.V.; Andriuli, F.J.; Cambell, W.C.; Hernandez, S.; Mochales, S.; Munguira, E. *Res. Vet. Sci.* (1990), **48**, 260. (d) Shoop, W.L.; Egerton, J.R.; Eary, C.H.; Suhayda, D. *J. Parasitol.* (1990), **76**, 349. (e) Ondeyka, J.G.; Goegel, R.T.; Schaeffer, J.M.; Kelemen, L.; Zitano, L. *J. Antibiot.* submitted for publication. (f) Wichmann, C.; Liesch, J. *J. Antibiot.* submitted for publication. (g) Blizzard, T.A.; Rosegay, A.; Mrozik, H.; Fisher, M.H. *J. Labelled Cmpds and Radiopharm.* submitted for publication.

3. Blizzard, T.A.; Marino, G.; Mrozik, H.; Fisher, M.H.; Hoogsteen, K.; Springer, J.P. *J. Org. Chem.* (1989), **54**, 2657.

4. Williams, R.M.; Glinka, T.; Kwast, E. *Tetrahedron Lett.* (1989), **30**, 5575.

5. Fredenhagen, A.; Hug, P.; Peter, H.H. *J. Antibiot.* (1990), **43**, 661.

6. Rosawsky, A. "Seven Membered Heterocyclic Compounds Containing Oxygen and Sulfur" Wiley-Interscience, 1972, p. 338.

7. (a) Cookson, R.C.; Liverton, N.J. *J. Chem. Soc., Perkin Trans I* , (1985), 1589. (b) Kocieński, P.; Love, C.; Whitby, R.; Roberts, D.A. *Tetrahedron Lett.* (1988), **29**, 2867. For some pioneering work in this area see also: (c) Chen, R.; Rowand, D.A. *J. Am. Chem. Soc.* (1980), **102**, 6609. (d) Nicolaou, K.C.; Claremon, D.A.; Barnette, W.E. *J. Am. Chem. Soc.* (1980), **102**, 6611.

8. Hutchins, R.O.; Hutchins, M.G.; Milewski, C.A. *J. Org. Chem.* (1972), **37**, 4190.

9. Clive, D.L.J.; Chittattu, G.; Curtis, N.J.; Kiel, W.A.; Wong, C.K. *J. Chem. Soc. Chem. Commun.* (1977), 725.

10. Bennington, F.; Morin, R.D.; Clarke, L.C., Jr. *J. Org. Chem.* (1959), **24**, 917.

11. Nicolaou, K.C.; Claremon, D.A.; Barnette, W.E.; Seitz, S.L. *J. Am. Chem. Soc.* (1979), ***101***, 3704.

12. (a) acetic anhydride, reflux, 100%. (b) fuming HNO_3, 0°-6°C, 54%. (c) N-acetylglycine, acetic anhydride, sodium acetate, 45°-65°C, 61%. (d) HCl, CH_3CO_2H, H_2O, reflux, 88%. (e) 30% H_2O_2, NaOH, 0°C, 97%. (f) H_2/Pd•C, CH_3CO_2H, 80°C, 82%. (g) BBr_3, CH_2Cl_2, -78°C, 100%. (h) prenyl bromide, K_2CO_3, DMF, 0°C, 61%.

13. All new compounds exhibited satisfactory ^1H NMR, IR, combustion analyses and/or high resolution mass spectra consistent with the assigned structures.

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