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SYNTHESIS OF A MONOCYCLIC ANALOGUE OF BIPOLAROXIN, A PHYTOTOXIN OF FUNGAL ORIGIN

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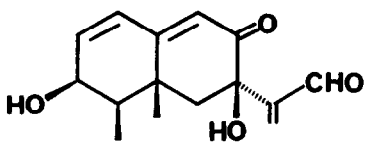
Abstract:

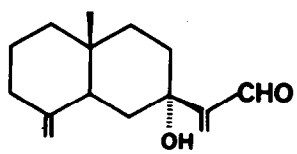
A sequence of three reactions leads to an efficient synthesis of compound **5**, a model for a newly discovered phytotoxic metabolite from a plant-pathogenic fungus Bipolaris cynodontis.

Phytotoxic and antifungal activities of sesquiterpene aldehydes from microbial sources are well documented in the literature.[1]

Of particular interest to us is bipolaroxin **7** a phytotoxic metabolite produced by Bipolaris cynodontis, a fungal pathogen of Bermuda grass.[2] Bipolaroxin has shown a remarkable host selectivity in the dose required to cause injury to this economically important weed.[2]



7: bipolaroxin



8 : 7–hydroxycostal

The B-ring of bipolaroxin has an interesting arrangement of functionalities. The analogous hydroxy-enal functionality of the sweet potato phytoalexin, 7-hydroxycostal **8**, has been implicated in the antifungal activity of this sesquiterpene aldehyde.[3] It therefore became of interest to establish whether the B-ring of bipolaroxin was alone responsible for the phytotoxic properties.

To test this possibility we have synthesised in three steps and 14% overall yield compound **5**,[4] a monocylic analogue of bipolaroxin. When sprayed as a 0.5% solution, compound **5** showed only weak (15-20%) inhibitory activity on two dicot weeds: velvetleaf (Abutilon theophrasti Medic.) and pigweed (Amaranthus albus L.), but no activity against grasses. Hence, the selective phytotoxicity of bipolaroxin is not exlusively dependent on the B-ring functionalities. On the other hand, compound 5 exhibited excellent antifungal activity (100% growth inhibition) against rice blast fungus (Piricularia oryzae) in culture suspension at 5 ppm.

The three steps involved in the synthesis of 5 were as follows:

(i) Mukaiyama-type aldol condensation[5] between selenoketone **1**[6] and silyl enol ether **2**[7] derived from 4,4-dimethyl 2-cyclohexen-1-one by reaction with TMS triflate.

(ii) [2,3] sigmatropic shift of the selenoxide generated in situ from the Mukaiyama product **3**[8] by treatment with hydrogen peroxide.

(iii) allylic oxidation of the rearranged product **4**[9] with selenium dioxide.

The simple methodology presented above should be generally applicable to the synthesis of bipolaroxin, 7-hydroxycostal and other sesquiterpene aldehydes.

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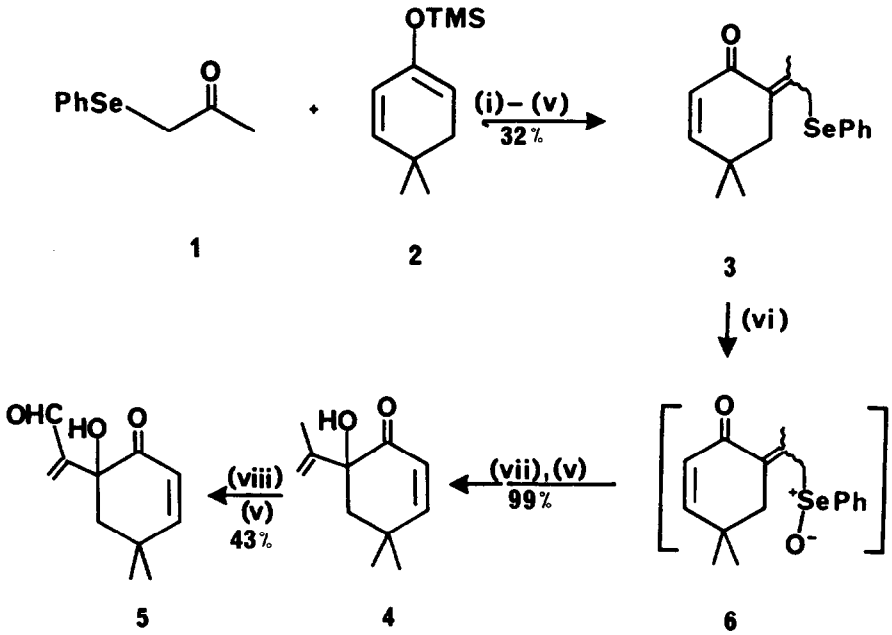

(i): CH_2Cl_2, N_2, -78° - 25°, 24h, (ii) -78°, H_2O, work-up with Et_2O, $MgSO_4$ (iii) Et_2O, N_2, 25°, pTSA, 18h, H_2O, (iv) work-up with Et_2O, $MgSO_4$, (v) silica gel chromatography, (vi) CH_2Cl_2, C_5H_5N, 30% H_2O_2, 0° - 25°, (vii) work-up with CH_2Cl_2, sat. Na_2CO_3, 1N HCl and brine, $MgSO_4$, (viii) 1,4-dioxane, SeO_2, reflux, 18h

References and Notes:

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2. F. Sugawara, G. Strobel, L. E. Fisher, G. D. Van Duyne and J. Clardy, Proc. Natl. Acad. Sci. U. S. A., 82 (24), 8291 (1985).

3. J. Schneider and K. Nakanishi, J. Chem. Soc., Chem. Commun., 352 (1983).

4. 6-Hydroxy-6-(2'propenal)-4,4-dimethyl-2-cyclohexen-1-one **5**: white amorphous solid; m.p. 112-114°C; ir cm^{-1} ($CDCl_3$) 3 700-3 100 and 1 660; NMR δ ppm ($CDCl_3$; 200 MHz) 9.56 (1H, s, CHO), 6.77 (1H, dd, J=1.47 and 10.3 Hz, H-3), 6.60 and 6.25 (2H, 2s, $C=CH_2$), 6.03 (1H, d, J=10.3 Hz, H-2), 3.1 (1H, bs, OH), 2.37 (1H, d, J=14.4 Hz, H-5), 1.87 (1H, dd, J=1.47 and 14.4 Hz, H-5), 1.31 and 1.13 (6H, 2s, $2CH_3$).

5. T. Mukaiyama, K. Bano and K. Narasaka, J. Am. Chem. Soc., **96**, 7503 (1974).

6. A. Toshimitsu, T. Aoai, H. Owada, S. Uemuraand M. Okano, J. Chem. Soc., Chem. Commun., 412 (1980).

7. 4,4-Dimethyl-2-cyclohexen-1-oxytrimethylsilane **2**: clear colourless liquid, b.p. 53-54° C/2.1 mmHg, ir cm^{-1} (thin film) 1670 and 1 650; NMR δ ppm ($CDCl_3$; 200 MHz) 5.56 and 5.55 (2H, 2s, H-2 and H-3) 4.79 (1H, m, 6-H), 2.12 (2H, d, J=4.6 Hz, 2H-5), 1.01 (6H, s, $2CH_3$) and 0.19 (9H, s, OTMS).

8. 6-(1'-Methyl-2'-phenylseleno)-4,4-dimethyl-2,6-exo-cyclohexadien-1-one **3**: pale yellow liquid; ir cm^{-1} (thin film) 1 650 and 1 600; NMR δ ppm ($CDCl_3$; 200 MHz) 7.57-7.16 (5H, m, C_6H_5Se), 6.53 and 6.45 (1H, 2d, J= 10.1 and 9.7 Hz, H-3), 5.83 and 5.75 (1H, 2d, J=10.1 and 10.2 Hz, H-2), 4.14 and 3.66 (2H, 2s, CH_2SePh), 2.42 and 2.25 (2H, 2s, 2H-5), 1.90 (3H, s, CH_31') and 1.06 and 0.98 (6H, 2s, $2CH_3$).

9. 6-Hydroxy-6-isopropylene-4,4-dimethyl-2-cyclohexen-1-one **4**: clear colourless oil; ir cm^{-1} (thin film) 3 600-3 200 and 1 670; NMR δ ppm ($CDCl_3$; 200 MHz) 6.60 (1H, dd, J=1.7 and 10.0 Hz, H-3), 6.03 (1H, d, J=10.0 Hz, H-2), 4.9 and 4.6 (2H, 2s, $C=CH_2$), 3.49 (1H, s, OH), 2.32 (1H, dd, J=1.66 and 14.16 Hz, 5-H), 1.88 (3H, s, $\underline{CH_3}C=CH_2$), 1.86 (1H, d, J=14.6 Hz, 5-H), 1.19 and 1.17 (6H, 2s, $2CH_3$).

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