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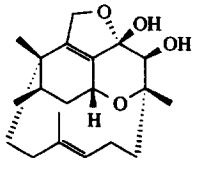
Synthetic Studies Towards Phomactin A. Concise Synthesis of the Novel Tricyclic Furanochroman System

Kevin M. Foote, Christopher J. Hayes and Gerald Pattenden*

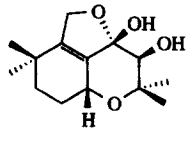
Department of Chemistry, Nottingham University, Nottingham NG7 2RD, England

Abstract: A concise synthesis of the tricyclic furanochroman unit **2** found in the unusual PAF antagonist phomactin A **1** is described. The synthesis is based on elaboration of the novel dihydrofuran enol ether **3** as key intermediate *via* the iodopyran **6** or the dihydrofuran **20**. Treatment of **3** with dimethyldioxirane in acetone-water then gave the furanochroman **2**.

Phomactin A **1** is a novel PAF antagonist recently isolated from the culture broth of marine fungus *Phoma sp.* (SANK 11486).[1] The moderately oxygenated diterpene natural product features an unusual furanochroman ring system **2**, making up part of a twelve membered macrocycle accommodating six stereogenic centres, two quaternary centres and a novel cyclic hemi-ketal forming part of a *syn* vicinal diol. Several structurally related metabolites sharing a common bicyclo [9.3.1] pentadecane ring system have been isolated from the same *Phoma sp.* and shown to have varying PAF-antagonist activities.[2,3] The unique structure of phomactin A, together with the implications that PAF may be involved in many inflammatory and respiratory diseases, attracted us to examine a total synthesis of the molecule and its congeners. In this communication we describe a synthesis of the tricyclic furanochroman **2** possessing all the oxygenation and sensitive functionality in phomactin A.



1



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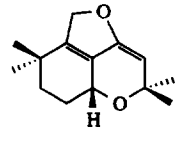
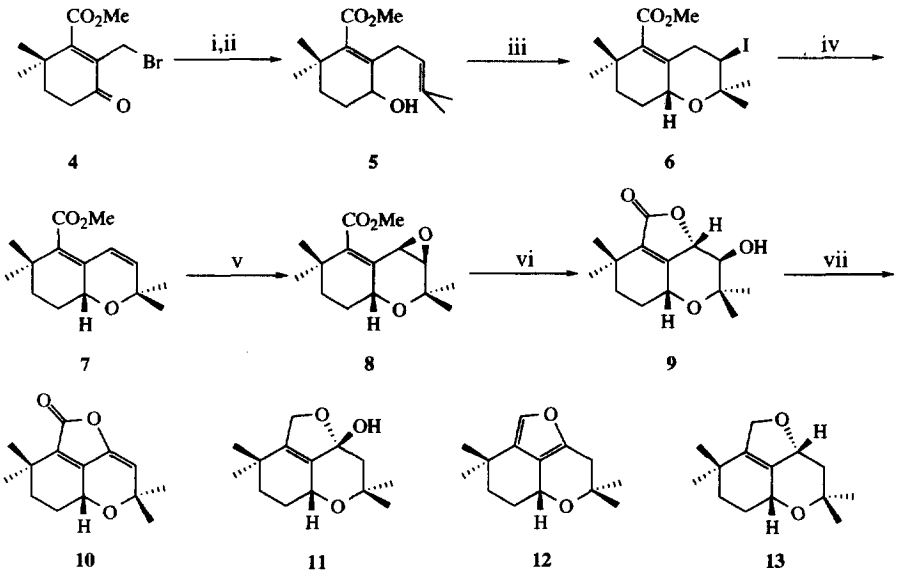


3

We investigated a synthesis of the tricyclic furanochroman **2** involving the dihydrofuran-based enol ether **3** as key intermediate. We planned initially to elaborate **3** by reduction of the ylidene-furanone **10** derived from the known bromo keto ester **4** (Scheme 1).[4] Thus, reduction of **4** using $NaBH_4$ in Et_2O-MeOH first produced the corresponding alcohol which by coupling with 2-methylprop-1-enyltributylstannane under Stille conditions[5,6] next gave the diene-alcohol **5**.[7] Iodoetherification[8] of **5** then gave the corresponding iodopyran **6** as a single diastereoisomer in 89% yield. Dehydroiodination of **6** using DBU, followed by treatment of the resulting diene ester **7** with mCPBA next produced a 3:2 mixture of diastereoisomers of the γ,δ-epoxy ester **8**,

which could be separated by chromatography. The lactonisation of **8** to the corresponding hydroxy furanone **9** was readily accomplished using hot $HClO_4$ in acetone-water.[9] An X-ray crystal structure determination confirmed the stereochemistry shown in the formula for **9**.[10] Dehydration of either diastereoisomer of the hydroxy-furanone **9** then led to the ylidene-furanone **10** in excellent yield. To our chagrin all attempts to reduce the ylidene-furanone **10** to the key enol ether intermediate **3** met with disappointment. Instead, the main products of reduction with DIBALH followed by $Et_3SiH/BF_3.OEt_2$[11] consisted of the cyclic hemi-acetal **11**, the substituted furan **12** (which is also produced when **11** is left standing for short periods of time), and the dihydrofuran **13**. We therefore developed an alternative route to the enol ether **3** which avoided acid conditions during the final stages in its synthesis. This route is shown in Scheme 2.

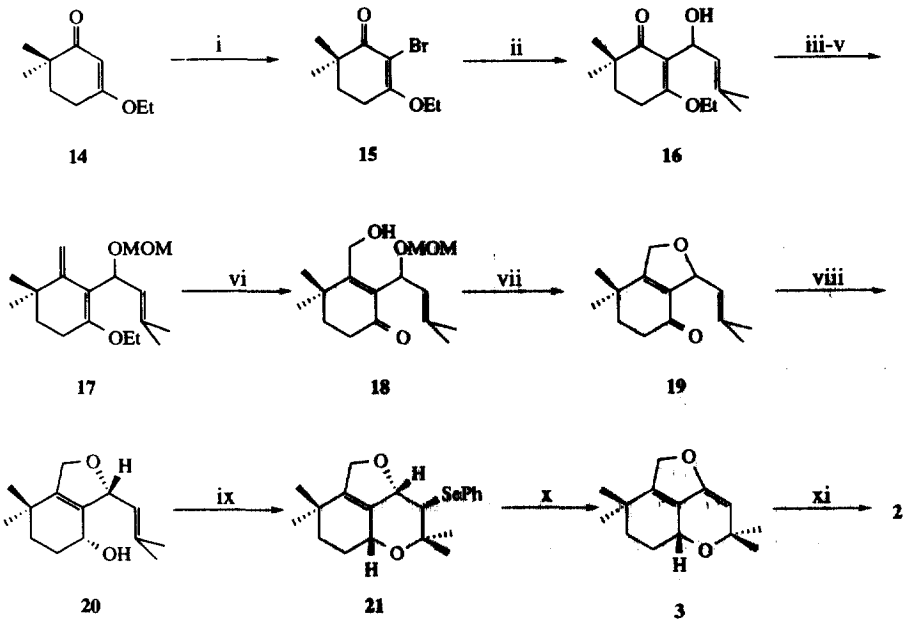


Reagents : i, $NaBH_4$, Et_2O, MeOH, 0°C, 52%; ii, $AsPh_3$, $Pd(dba)_3$, $Me_2C{:}CHSnBu_3$, THF, Δ , 66%; iii, I_2, $NaHCO_3$, MeCN, 0°C, 89%; iv, DBU, THF, RT, 76%; v, mCPBA, CH_2Cl_2, RT, 35%; vi, $HClO_4$, Me_2CO, H_2O, Δ, 49%; vii, I_2, Ph_3P, imidazole, PhMe, Δ, 87%

Scheme 1

Thus, bromination[12] of the known vinylogous ester **14**,[13] followed by metallation of the resulting bromo derivative **15** and quenching with 3-methylbut-2-enal first gave the substituted allylic alcohol **16**. After protection of **16** as its MOM ether, a Peterson methylenation[14,15] next led to the unstable diene ether **17**. Treatment of the enol ether **17** with mCPBA then gave the 3-hydroxymethyl substituted cyclohexenone **18**, which immediately cyclised to the dihydrofuran **19** in the presence of camphor sulphonic acid. Reduction of the carbonyl group in **19**, using DIBALH in toluene at -78°C, led to a 1:1 mixture of α- and β-hydroxy epimers of the alcohol **20** which could be separated by chromatography. A Mitsunobu inversion[16] of the β-hydroxy epimer corresponding to **20**, led to **20** in 66% overall yield. Treatment of the unsaturated alcohol **20** with phenylselenyl

bromide resulted in smooth cyclisation[17] to a single diastereoisomer of the furanochroman **21** in 77% yield, which we tentatively assigned the stereochemistry shown. Finally, oxidation of **21** using mCPBA in CH_2Cl_2 at



Reagents : i, NBS, CCl_4, 70%; ii, tBuLi, THF, -90°C; 3-methylbutenal, -78°C, 56%; iii, MOMCl, $EtNiPr_2$, CH_2Cl_2, Δ, 90%; iv, TMSMeLi, Et_2O, 0°C; v, KH, THF, RT; vi, mCPBA, EtOH, RT, 31%; vii, CSA, CH_2Cl_2, RT, 91%; viii, iBu_2AlH, PhMe, -78°C, 46%; ix, PhSeBr, Et_3N, CH_2Cl_2, -78°C, 77%; x, mCPBA, CH_2Cl_2, 0°C; THF, KOH, Δ; xi, DMDO, Me_2CO, H_2O, 22%

Scheme 2

0°C, followed by base-catalysed elimination of the elements of phenylselenic acid from the intermediate selenoxide, produced the desired enol ether dihydrofuran **3** as an unstable oil. When the enol ether **3** was treated with a solution of dimethyldioxirane[18] in acetone-water it gave the required *syn*-(β,β)-vicinal diol **2** and its corresponding *anti*-(β,α)-epimer as colourless solids which were easily separated by chromatography. The *syn*-diol tricyclic furanochroman **2** displayed nmr spectroscopic data which correlated closely with corresponding matching resonances published for natural phomactin A **1**.[19] Studies are now in progress towards a total synthesis of phomactin A, building on the principles described in this communication.

Acknowledgements

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References and Notes

1. Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H., *J.Am.Chem.Soc.* **1991**, *113*, 5463.
2. Chu, M.; Truumees, I.; Gunnarsson, I.; Bishop, W. R.; Kreutner, W.; Horan, A. C.; Patel, M. G., *J.Antibiotics.* **1993**, 554.
3. Sugano, M.; Sato, A.; Iijima, Y.; Furuya, K.; Haruyama, H.; Yoda, K.; Hata, T., *J.Org.Chem.* **1994**, *59*, 564.
4. Heather, J. B.; Mittal, R. S. D.; Sih, C. J., *J.Am.Chem.Soc.* **1976**, *98*, 3661.
5. Stille, J. K., *Angew.Chem.Internat.Ed.Engl.* **1986**, *25*, 508.
6. Farina, V.; Krishnan, B., *J.Am.Chem.Soc.* **1991**, *113*, 9585.
7. Satisfactory spectroscopic data, together with mass spectrometry and/or microanalysis data were obtained for all new compounds.
8. Bartlett, P. A.; Ting, P. C., *J.Org.Chem.* **1986**, *51*,2230.
9. Begley, M. J.; Bowden, M. C.; Patel, P.; Pattenden, G., *J.Chem.Soc., P1,* **1991**, 1951.
10. We thank the late Dr M.J.Begley (deceased 28.2.94) for this X-ray structure determination; full details will be published in a later communication. Treatment of the diastereoisomer of **8** with hot $HClO_4$ in Me_2CO-H_2O led to the corresponding α-(C*H* of furanone) epimer of the hydroxy furanone **9**.
11. Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K., *J.Org.Chem.* **1981**, *46*, 2417.
12. Belmont, D. T.; Paquette, L. A., *J.Org.Chem.* **1985**, *50*, 4102.
13. Quesada, M. L.;Schlessinger, R. H., *Synth.Commun.* **1976**, *6*, 555.
14. Wege, P. M.; Clark, R. D.;Heathcock, C. H., *J.Org.Chem.* **1976**, *41*, 3144.
15. Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I., *Tetrahedron,* **1992**, *48*, 6975.
16. Mitsunobu, Y., *Synthesis,* **1981**, 1.
17. Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M., *J.Am.Chem.Soc.* **1980**, *102*, 3784.
18. Adam, W.; Bialas, J.;Hadjiarapoglou, L., *Chem.Ber.* **1991**, *124*, 2377.
19. Less polar isomer. ^{1}H NMR (500MHz,$CDCl_3$) 4.80(dd,1H,*J* 12.9 and 2.8Hz,5*H*), 4.41(dd,1H,*J* 12.9 and 1.3Hz,5*H*), 4.33(m,1H,8a*H*), 3.80(s,1H,3aO*H*), 3.56(d,1H,*J* 6.0Hz,3*H*), 2.81(d,1H,*J* 6.0Hz,3O*H*), 2.04-2.07 (m,1H,8*H*),1.51-1.57(m,3H,7*H* and 8*H*), 1.31(s,3*H*), 1.30(s,3*H*), 1.11(s,3*H*), 1.08(s,3*H*); ^{13}C NMR (125.8MHz,$CDCl_3$) 146.1(s), 130.1(s), 105.9(s), 79.4(d), 75.5(s), 71.6(t), 64.1(d),36.7(t), 31.9(s), 28.8(q), 28.4(q), 26.7(t), 26.0(q), 17.7(q); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (M-OH)$^+$ 237.1491, found 237.1472. More polar isomer. ^{1}H NMR (500MHz,$CDCl_3$) 4.82(dd,1H,*J* 13.1 and 2.9Hz,5*H*), 4.48(dd,1H,*J* 13.1 and 1.4Hz, 5*H*), 4.34(m,1H,8a*H*), 3.43(d,1H,*J* 2.0Hz,3*H*), 2.57(s,1H,3aO*H*), 2.31(d,1H,*J* 2.3Hz,3O*H*), 2.04-2.09(m,1H,8*H*), 1.57-1.66(m,3H,7*H* and 8*H*), 1.45(s,3H), 1.33(s,3H), 1.14(s,3H), 1.08(s,3H); ^{13}C NMR (125.8MHz,$CDCl_3$) 147.1(s), 128.5(s), 107.5(s), 76.2(d), 75.1(s), 72.1(t), 64.3(d), 36.8(t), 32.2(s), 28.6(q), 27.3(q), 26.9(t), 26.1(q), 22.9(q); HRMS (EI+) calcd for $C_{14}H_{20}O_3$ (M-H_2O)$^+$ 236.1412, found 236.1443.

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