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A SYNTHESIS OF *pseudo*-GLOEOSPORONE

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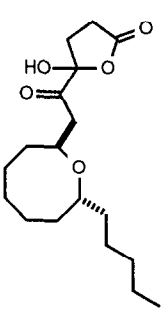
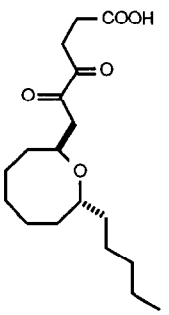
Summary: *The trans-2,8-disubstituted oxocane (2) was synthesized and shown not to be the natural product gloeosporone.*

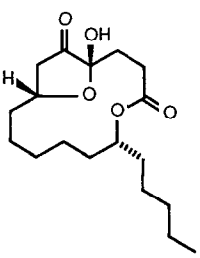
A metabolite which inhibits seed germination was isolated from the spores of the fungus *Colletotrichum gloeosporioides* and given the trivial name gloeosporone[1]. Meyer and co-workers[2] assigned the structure (1)[3] on the basis of IR, ^{1}H- and ^{13}C-NMR and MS data. However, recent synthetic studies[4,5] have shown that the putative structure (1) is incorrect. A revised structure derived from detailed analysis of the 500 MHz ^{1}H NMR data and a single crystal x-ray analysis has revealed that gloeosporone is the 14-ring oxygen-bridged macrolide (3)[6]. We now describe our attempts to synthesise *pseudo*-gloeosporone (1) and show that it exists preferentially as the open-chain tautomer (2). Key steps in our approach were the use of an intramolecular Mukaiyama directed aldol condensation[7] to construct the oxocane ring and the photo-oxidation of the silylfuran (13) to give the γ-keto-acid (15).



(1)



(2)



(3)

In our synthesis of *pseudo*-gloeosporone outlined in the Scheme we used the 8-endo$_e$endo$_n$ cyclisation[8] of the enol silane (4) to give the oxocan-4-one (5). Although the yield of the cyclisation was modest, the product was obtained as a single diastereoisomer and was easily separated from the highly polar by-products by column chromatography. The preferential formation of the 8-membered ring instead of the alternative 10-membered ring is noteworthy.

Competing elimination of the ring oxygen foiled several standard methods for the reduction of ketone group in (**5**) to the corresponding alkane (**10**). Despite its length, the 5-step procedure used was reasonably efficient and gave (**10**) in 70% overall yield from (**5**).

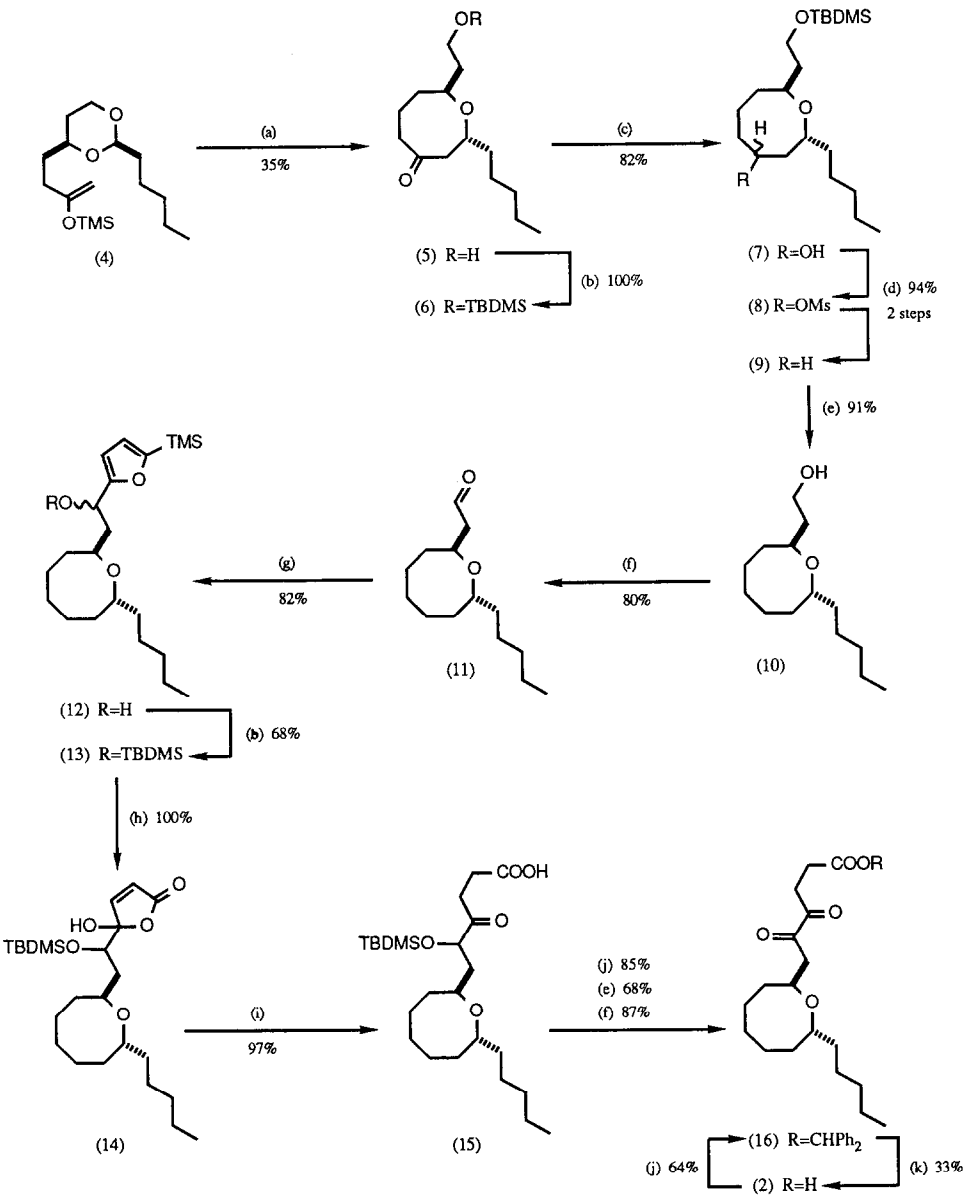
Synthesis of the aldehyde (**11**)[10] and its subsequent elaboration to the γ-keto acid of *pseudo*-gloeosporone was likewise complicated by competing elimination of the ring oxygen. In the Swern oxidation[9] of (**10**) this problem was minimised by using N-methylmorpholine as the base instead of the usual triethylamine.

The trimethylsilyl furan (**12**) was readily prepared from aldehyde (**11**) and provided a particularly mild and convenient Trojan horse for the introduction of the γ-keto acid moiety after more direct and brutal methods failed. Photo-oxidation of the furan (**13**) gave the 5-hydroxybutenolide (**14**) which existed predominantly as the ring tautomer (IR: 3180 and 1760 cm^{-1}; ^{13}C=O at δ170.76). However, on reduction of the double bond the γ-keto acid (**15**) was obtained predominantly as the open chain tautomer.

The diphenylmethyl ester (**16**)[11] of *pseudo*-gloeosporone was obtained as a single diastereoisomer by a 3-step sequence from (**15**). The structure (**16**) was corroborated by the three carbonyl peaks in the IR (1745, 1725, and 1720 cm^{-1})and the three carbonyl peaks in the ^{13}C-NMR spectrum (δ198.23, 197.76, and 171.36). Hydrogenolysis of the diphenylmethyl ester under standard conditions gave *pseudo*-gloeosporone[12] as a yellow-green oil. The IR spectrum revealed typical carboxylic acid absorptions at 3600-2500 and 1720 cm^{-1} and two much weaker peaks at 1790 and 1760 cm^{-1}. The ^{13}C NMR spectrum showed a broadened signal at δ176.77 due to the carboxylic acid and the two carbonyls of the α-diketone had coalesced to give a single weak and broadened peak at δ198.72. The remaining fifteen signals were sharp. Similarly, some of the signals of the 360 MHz ^{1}H NMR spectrum were broadened. These data suggest that *pseudo*-gloeosporone undergoes ring-chain tautomerism and that the chain tautomer predominates. Proof that nothing untoward occurred during the final hydrogenolysis step was obtained by converting (**2**) back to the diphenylmethyl ester on treatment with diphenyldiazomethane.

The work reported herein provides a useful illustration of the potential of intramolecular directed aldol reactions for the construction of 8-membered rings[13] and makes a tardy contribution to the final structure elucidation of gloeosporone.

Acknowledgements. We thank Professor W. L. Meyer (University of Arkansas) for supplying us with information regarding the reassigned structure of gloeosporone and Professor Stuart Schreiber (Yale University) for generous provision of spectral data. We also thank Dr. Richard Whitby and Mrs Joan Street for NMR experiments and Dow Corning Ltd. and the SERC for financial support.



Reagents and conditions: (a) $TiCl_4$ / CH_2Cl_2, -78°C, 5 min; (b) TBDMSCl, imidazole / DMF, r.t.; (c) $NaBH_4$ / MeOH, 0°C, 40 min; (d) MsCl / CH_2Cl_2, -20°C, 5 min followed by $LiBHEt_3$ / THF, reflux 3 h; (e) Bu_4NF/ THF, r.t.; (f) Swern oxidation; (g) 5-lithio-2-trimethylsilylfuran / THF, -78°C, 25 min; (h) O_2, methylene blue, hν / MeOH, -40°C, 10 min; (i) H_2, 5% Rh/Al_2O_3 in EtOAc, r.t.; (j) Ph_2CN_2 / benzene, reflux; (k) H_2, 5% Pd/C in EtOAc.

Scheme

TBDMS = t-$BuMe_2$ Si ; TMS = Me_3 Si

References and Notes

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3. Stereochemistry was undefined.

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9. A. Mancuso, S.-L. Huang, and D. Swern, *J.Org. Chem.*, 1978, **43**, 2480.

10. Data for (**11**): IR (CCl_4) 2940s, 2880s, 2740w, 1730s, 1110s, and 1090s cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) 9.75 (1 H, t, J 2.4 Hz), 4.04 (1 H, m), 3.48 (1 H, m), 2.65 (1 H, ddd, J 15.4, 8.2, and 2.8 Hz), 2.40 (1 H, ddd J 15.7, 4.1, and 2.1 Hz), 1.9-1.2 (18 H, m), 0.89 (3 H, t, J 6.3 Hz).

11. Data for (**16**): IR (CCl_4) 3070w, 3040w, 2930s, 2860s, 1745s, 1725s, 1720s, 1200s, 1185s, 1165s, 1090s, 705s cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) 7.33 (10 H, m), 6.90 (1 H, s), 4.05 (1 H, m), 3.45 (1 H, m) 3.14 (1 H, dt, J 19.2, 7.2 Hz), 3.10 (1 H, dd, J 16, 7.6 Hz), 3.02 (1 H, dt, J19.3, 7.2 Hz), 2.77 (2 H, ddd, J 9.6, 6.1, 3.0 Hz), 2.64 (1 H, dd, J 16, 4.6 Hz), 1.88-1.06 (18 H, m), 0.88 (3 H, t, J 6.7 Hz); ^{13}C NMR (90 MHz) 198.23 (s), 197.76 (s), 171.36 (s), 140.26 (s), 128.67 (d), 128.11 (d), 127.33(d), 79.88 (d), 77.59 (d), 75.32 (d), 43.30 (t), 36.87 (t), 33.93 (t), 33.51 (t), 32.15 (t), 31.21 (t), 28.17 (t), 27.05 (t), 25.96 (t), 24.16 (t), 24.05 (t), 22.78 (t), 14.16 (q).

12. Data for (**2**): IR ($CDCl_3$) 3600-2500br, 2960s, 2880s, 1790m, 1760m, 1720s, 1090m cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) 7.97 (1 H, br s), 4.05 (1 H, m), 3.48 (1 H, m), 3.14 (1 H, dd, J 15.1, 8.9 Hz), 3.06-2.50 (3 H, m), 2.68 (2 H, t, J6.6 Hz), 1.90-110 (18 H, m), 0.88 (3 H, t, J6.5 Hz), ^{13}C NMR (90 MHz) 198.72 (br s), 176.77 (br s), 80.09 (d), 75.93 (d), 43.39 (t), 36.68 (t), 33.64 (t), 33.51 (t), 32.12 (t), 30.79 (t), 27.74 (t), 26.95 (t), 25.92 (t), 24.02 (t), 23.94 (t), 22.74 (t), 14.16 (q); UV (EtOH) 260nm (e 507), 418nm (e 23); m/z 326 (M^+, 1.2 %), 282 (0.3), 225 (5), 207 (8), 183 (20), 165 (18), 109 (27), 55 (100).(Found: M^+, 326.2095. $C_{18}H_{30}O_5$ requires M, 326.2085).

13. For some alternative recent methods used to construct the oxocane ring system see : S. L. Schreiber and S. E. Kelly, *Tetrahedron lett., 1984, 25*, 1757; R. W. Carling and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*,1986, 565; K. C. Nicolaou, C.-K. Hwang, M. E. Duggan, K. B. Reddy, B. E. Marron, and D. G. McGarry, *J. Am. Chem. Soc.*, 1986, **108**, 6800; K. C. Nicolaou, D. G. McGarry, P. K. Somers, C. A. Veale, and G. T. Furst, *J. Am. Chem. Soc.*, 1987, **109**, 2504.

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