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STUDIES ON THE SYNTHESIS OF GLOEOSPORONE - SYNTHESIS OF THE PROPOSED 2,8-DISUBSTITUTED OXOCANE STRUCTURE

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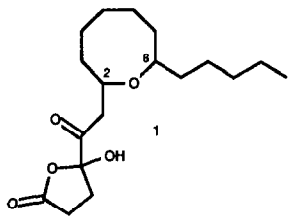
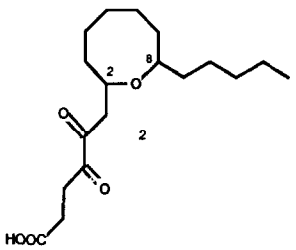
Summary: Gloeosporone is neither the cis- nor the trans-2,8-disubstituted oxocane (1) nor its tautomer (2) whose total syntheses are described in this Letter.

Gloeosporone, a germination self-inhibitor from Colletotrichum gloeosporioides was isolated in 1982,[1] and assigned the structure (1) by Meyer and co-workers in 1983.[2]



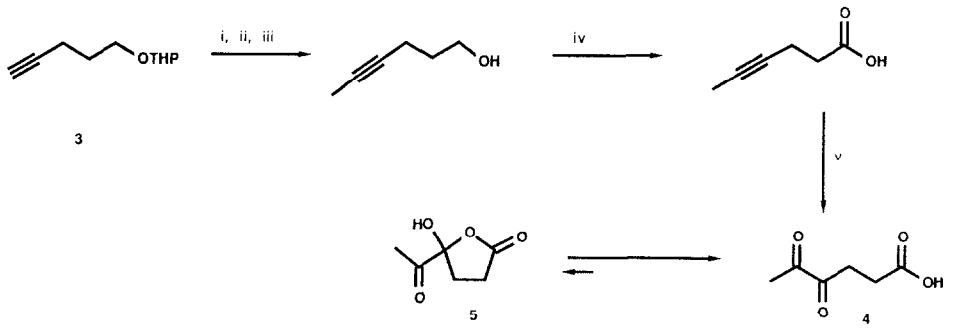
1



2

Neither relative nor absolute stereochemistry was assigned to (1), and we were attracted by the possibility of solving these questions by using our recently developed method for the synthesis of 2,8-disubstituted oxocanes.[3] We were furthermore intrigued by the δ5.06 ^{1}H N.M.R. resonance assigned to the methine proton at C-8 and by the question of the nature of the equilibrium between (1) and its open chain tautomer (2). γ,δ-Diketo-acids are virtually unknown compounds, and we chose to prepare the simplest conceivable member of this family, 4,5-diketohexanoic acid (4) in order to examine the tautomeric equilibria (e.g. with 5) potentially available to this compound. The synthesis is summarised in Scheme 1. The first step was methylation of the anion of the THP ether of 4-pentynol (3). After deprotection and Jones oxidation of the alcohol the triple bond in the resulting 5-hexynoic acid was oxidised to an α-diketone using a known procedure[5] based on catalytic ruthenium tetroxide, but under the modified solvent conditions reported by Sharpless in another context.[6]

Scheme 1

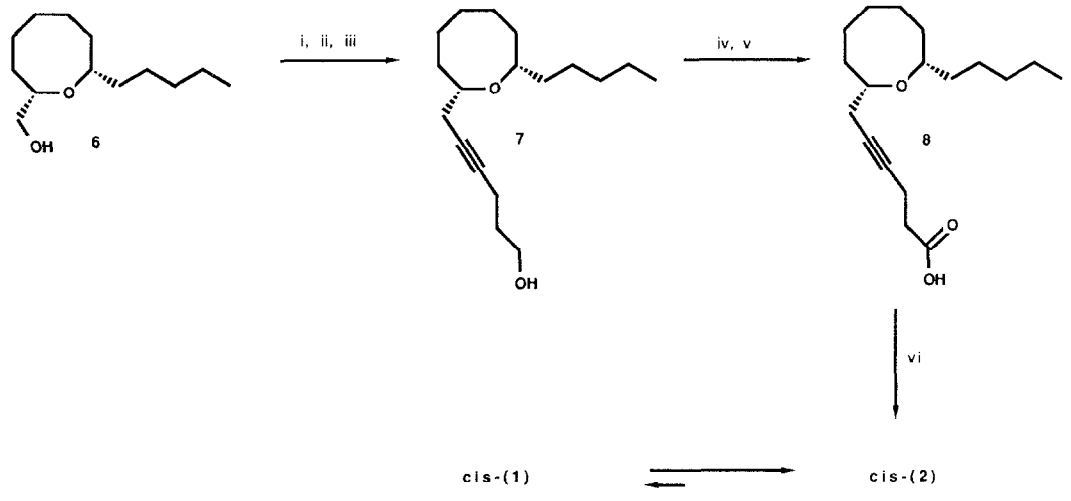


Reagents: i, n-BuLi, TMEDA, THF, 0 °C; ii, MeI, 0 °C; iii, PTSA, MeOH (38% overall); iv, Jones[4] reagent, Et_2O (53%); v, RuO_2, $NaIO_4$, MeCN, CCl_4, H_2O (40%).

The acid (**4**) apparently prefers the open chain form rather than the tautomeric pseudo-acid structure (5) as evidenced by the I.R. spectrum and the ^1H and ^{13}C NMR spectra.[7] Although such tautomeric equilibria in γ,δ-diketo-acids appear not to have been previously studied, related phenomena in γ-keto-acids have been reported by Chadwick and co-workers.[8]

With this result in hand we proceeded to the synthesis (Scheme 2) of the cis-isomer of (**1**). The readily available cis-hydroxymethyloxocane (**6**)[3] was

Scheme 2

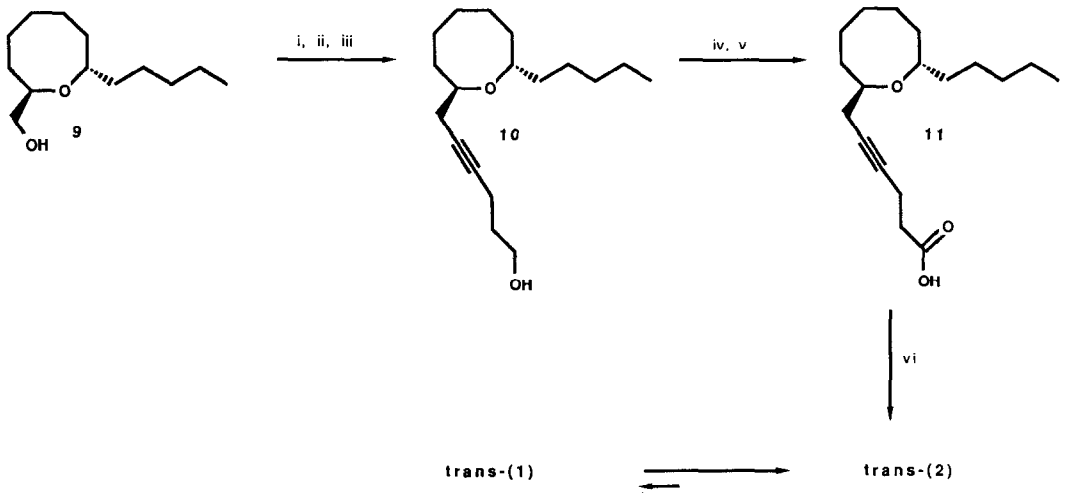


Reagents: i, $(CF_3SO_2)_2O$, DMAP, CH_2Cl_2, 0 °C; ii, n-BuLi, (3), THF; iii, PTSA, MeOH, (49% overall); iv, PCC, CH_2Cl_2; v, Jones reagent, Et_2O, (84%); vi, "RuO_4" (60%)

converted into the corresponding triflate ester which was then alkylated with the anion derived from (3). The remaining steps closely resembled those reported in the model study, and included the acetylenic alcohol (7) and acid (8) as key intermediates. Ruthenium tetroxide oxidation of (8) gave cis-(2) which was isolated as a relatively unstable oil,[9] whose physical and spectroscopic properties[10] did not match those reported.[2] In particular the methine protons at C-2 and C-8 were observed as complex broad multiplets at δ 3.4 and 3.6 and δ3.95 and 4.05 in the ^{1}H N.M.R. spectrum which suggested an approximately 3:1 equilibrium mixture of cis-(2) and cis-(1).

Methine proton resonances for trans-2,8-disubstituted oxocane derivatives exhibit a downfield trend compared to the corresponding cis-compounds,[3] and it was considered necessary to synthesise trans-(1) as a possible structure for gloeosporone. The synthesis (Scheme 3) closely parallels the corresponding cis-series. The starting material was the available trans-disubstituted oxocane (**9**) which was converted via the key intermediates (**10**) and (**11**) into the relatively unstable[9] trans-(2) which existed in equilibrium (ca. 2:1) with trans-(1) as an oil. The methine protons at C-2 and C-8 occurred at δ3.65 and 3.75 and δ4.21 and 4.11 in the ^{1}H N.M.R. spectrum.[11]

Scheme 3



Reagents: i, $(CF_3SO_2)_2O$, DMAP, CH_2Cl_2, 0 °C; ii, n-BuLi, (3), THF; iii, PTSA, MeOH (50% overall); iv, PCC, CH_2Cl_2; v, Jones reagent, Et_2O (41%); vi, "RuO_4" (68%)

In conclusion the total synthesis of both cis- and trans- (2)⇌(1) has established that these are not the correct structures for gloeosporone.[12]

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References and Footnotes

1. A. R. Lax, G. E. Templeton, and W. L. Meyer, Phytopathology, 1982, **74**, 503.
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4. K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, J. Chem. Soc., 1946, 39.
5. H. Gopal and A. J. Gordon, Tetrahedron Lett., 1971, 2941.
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7. Selected spectroscopic data for (**4**). I.R. ($CHCl_3$) 1780 (weak), 1710 (strong) cm^{-1}, ^1H N.M.R. ($CDCl_3$) δ2.35 (3H, s), 2.70 (2H, t, J 6.1 Hz), 3.04 (2H, t, J 6.1 Hz), 7.8-9.0 (1H, broad singlet); ^{13}C N.M.R. (CD_2Cl_2, -80 °C) δ 23.69, 26.67, 29.96, 179.09, 196.23, 196.38.
8. D. J. Chadwick and J. D. Dunitz, J. Chem. Soc., Perkin Trans. 2, 1979, 276; D. J. Chadwick, S. N. Whittleton, and R. W. H. Small, ibid, 1982, 669; D. J. Chadwick, W. B. Schweizer, P. Seiler, and S. N. Whittleton, Acta Cryst., 1982, **B38**, 1043.
9. The apparent instability of cis- and trans-(**1**) may be due to the presence of trace quantities of ruthenium salts in the reaction product.
10. Selected[13] spectroscopic data for cis-(**2**): I.R. ($CHCl_3$) 3520 (weak), 3400-2400 (broad), 1715 (strong) cm^{-1}; ^1H N.M.R. ($CDCl_3$) δ 0.86 (3H, m), 1.1-1.3 (18H, complex multiplets, CH_2 envelope), 2.4-2.8 (4H, m), 2.9-3.2 (2H, m), 3.6 (1H, broad m), 4.05 (1H, broad m).
11. Selected[13] spectroscopic data for trans-(2): I.R. ($CHCl_3$) 3500 (weak), 3400-2400, (broad), 1715 (strong) cm^{-1}; ^1H N.M.R. ($CDCl_3$) δ0.85 (3H, m), 1.1-1.75 (18H, complex multiplets, CH_2 envelope), 2.3-2.6 (2H, m), 2.65-3.05 (4H, m,), 3.75 (1H, broad m), 4.11, (1H, broad m).
12. During the course of this work we learned of the independent synthesis of cis-(**2**) by S. E. Kelly and S. L. Schreiber (manuscript in preparation). We thank Professor Schreiber for a free and generous exchange of information.
13. Other signals were present which were attributable to (**1**) but only those signals of the major tautomer (**2**) are listed for the sake of simplicity.

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