# Synthesis of Medium Ring Ethers. Part 3.† Disproof of the Proposed 2,8-Disubstituted Oxocane Structure for Gloeosporone. Synthesis of *pseudo*-Gloeosporone

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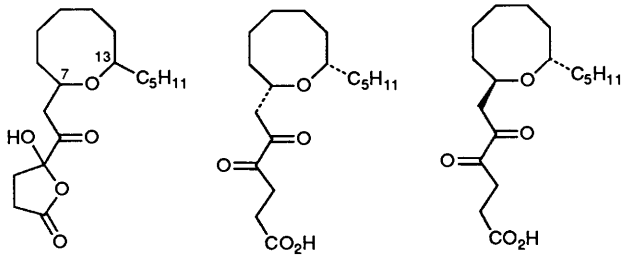
Synthesis of the *cis*- and *trans*-2,8-disubstituted oxocane derivatives **2** and **3** (carrying the unusual γ,δ-diketohexanecarboxylic acid side chain) by ozonolysis of the alkynes **14** and **18** (prepared respectively from the alcohols **11** and **15**) demonstrated unequivocally that neither of these compounds nor their hydroxy-γ-lactone ring (lactol) tautomers **1** corresponded to the naturally occurring fungal self germination inhibitor gloeosporone. A study of 4,5-dioxohexanoic itself **9** revealed a remarkably low tendency to exist as its hydroxy-γ-lactone (lactol) tautomer **10**.

In 1982 gloeosporone, a germination self inhibitor, was isolated from *Colletotrichum gloeosporioides*[1] and the following year Meyer and co-workers proposed the intriguing oxocane structure **1** for this antifungal metabolite.[2] Until that time the monocyclic oxocane ring skeleton had only been observed in marine natural products of the *Laurencia* family.[3] In view of the novel structure proposed for gloeosporone and its intriguing biological activity, we became interested in its total synthesis using our recently developed method for *cis*- and *trans*-2,8-disubstituted oxocanes[4] in order to establish its relative and absolute stereochemistry.[5] Contributions from various research groups to the synthesis of oxocanes have been impressive,[6] and two other groups in particular have addressed the question of the synthesis of **1** (named *pseudo*-gloeosporone).[7,8]



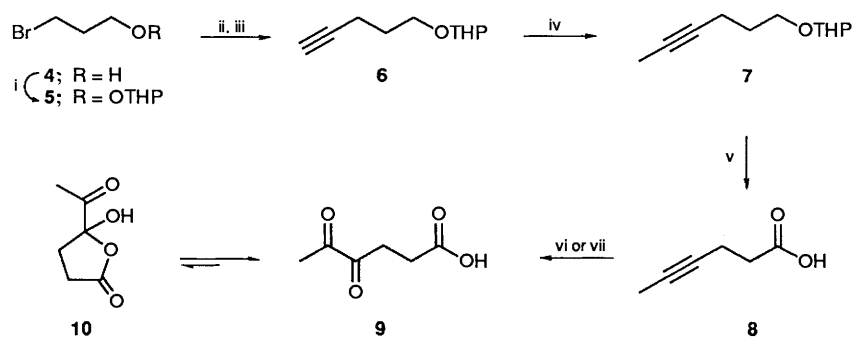

**1** **2** **3**

A particular feature of the $^1H$ NMR spectral assignments for the oxocane **1** was the remarkably low field signal (δ 5.06) assigned to the proton at C-13, whereas our experience (which was being accumulated) at the outset of this investigation indicated a much more reasonable range for such protons was δ 3.5–3.9.[1,4b] The observed chemical shift of the proton attached to C-13 is much more characteristic of the environment created by an *O*-acyl substituent. However it was possible that the intriguing 5-hydroxy-5-ketolactone side chain of **1**, which was an essential component of the structural assignment, could induce a downfield chemical shift of the proton in question; significantly, virtually nothing was known at the outset of this work about such compounds nor about the ring chain tautomerism of γ,δ-dioxocarboxylic acids with respect to the position of equilibrium and preference for ring size of the cyclic tautomer.

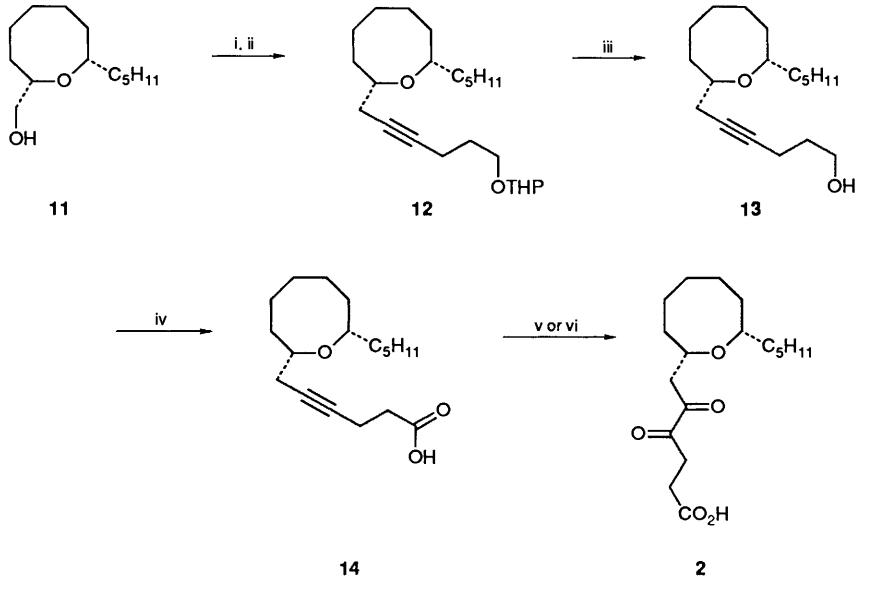
Our first aim therefore was to prepare 4,5-dioxohexanoic acid **9** and study the ring-chain tautomerism of this compound. We chose to prepare the 1,2-diketone functionality by oxidation of hex-4-ynoic acid **8**. Although alkylation of the dianion of pentynoic acid[9] was a possible route for the preparation of the required alkyne **8** and also for introduction of the functionality into the side chain of a suitable hydroxymethyloxocane, we chose to follow a more conventional route involving the preparation and subsequent oxidation of the hex-4-ynol derivative **7** (Scheme 1). The anion of the tetrahydropyranyl (THP) protected pent-4-ynol **6** was alkylated with methyl iodide. The product was deprotected and the resulting alcohol was oxidised with Jones reagent[11] to give the required hexynoic acid **8**. Initially we explored the ruthenium tetroxide oxidation of the acetylene to the 1,2-diketone. Such a reagent has been used for the oxidation of simple alkynes;[12] in view of the presence of the carboxylic acid in **8** we modified the conditions in accord with the Sharpless protocol,[13] and obtained the required carboxylic acid **9** in 40% yield. However we found that this product was prone to decomposition, which we attributed to the presence of trace quantities of ruthenium salts. Such a side reaction does not seem to have been encountered by Seebach, who has independently developed the ruthenium dioxide/sodium periodate oxidation as a quite general method for the preparation of 1,2-diketones.[14] Because of the complications arising from the use of ruthenium tetroxide we turned to ozonolysis[15] which afforded the required dioxohexanoic acid in excellent yield. Significantly, in our hands, the dioxohexanoic acid showed very little tendency to cyclise to the lactol tautomer **10**, as indicated by the simple $^1H$ NMR spectrum (see Experimental section), the presence of a weak band at ν 1780 $cm^{-1}$ and a much stronger band at ν 1710 $cm^{-1}$ in the solution IR spectrum, and conclusively the low temperature $^{13}C$ NMR spectrum which shows the clear presence of three carbonyl carbon atoms at δ 196.38, 196.23 and 179.09 as well as three characteristic saturated carbon resonances. The low temperature spectrum was necessary owing to the ambiguity in the room temperature spectrum in the number of carbonyl carbon resonances present. Also when the spectrum was recorded at low temperature we were able to exclude rigorously the possibility of an intermediate exchange phenomenon, as has been discussed by Dunitz, Chadwick and others in their study of γ-keto acids,[16] and the evidence unambiguously demonstrates that <5% of the cyclic tautomer **10** is present at this temperature. A similar conclusion has been reached independently by Meyer, Seebach and Schreiber.[17]

We then turned our attention to applying this strategy to the synthesis of the oxocanes **2** and **3**. The *cis*-hydroxymethyloxocane **11** is available by the Tebbe methylenation/hydroboration sequence on the corresponding 7-pentylheptanolide as previously reported.[4a,b] Displacement of the *O*-trifluoromethanesulfonate (triflate) with the lithium derivative of the alkyne

† Part 2: Preceding paper.




**Scheme 1** *Reagents:* i, Dihydropyran, toluene-*p*-sulfonic acid, toluene (reflux);[10] ii, Li-C≡C-$SiMe_3$ (prepared from BuLi and H-C≡C-$SiMe_3$), *N,N,N′N′*-tetramethylethylenediamine (TMEDA), tetrahydrofuran (THF), 60 °C; iii, tetrabutylammonium fluoride (TBAF), THF, 0 °C (70% from **5**); iv, BuLi, TMEDA, THF 0 °C, followed by MeI (70%); v, TsOH, MeOH (95%), followed by Jones reagent[11] (53%); vi, $RuO_2$ (catalytic), $NaIO_4$, $H_2O$, $CCl_4$, MeCN, 0 °C (40%); vii, $O_3$,[15] MeOH, −65 °C (77%)

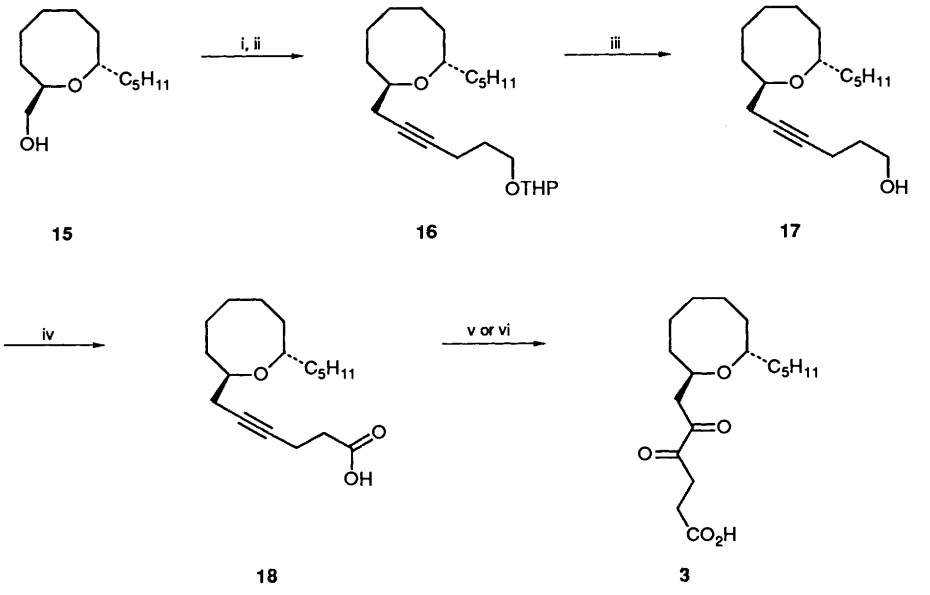



**Scheme 2** *Reagents:* i, Trifluoromethanesulfonic anhydride ($Tf_2O$), 4-dimethylaminopyridine (DMAP), $CH_2Cl_2$, 0 °C (83%); ii, **6**, BuLi, THF, room temperature (80%); iii, TsOH, MeOH, room temperature, 14 h (91%); iv, pyridinium chlorochromate (PCC), $CH_2Cl_2$, followed by Jones reagent in ether, room temperature (80%); v, $O_3$, $CH_2Cl_2$, −65 °C (100%); vi, $RuO_2$ (catalytic), $NaIO_4$, $H_2O$, $CCl_4$, MeCN, 0 °C

**6** afforded the homologated product **12** in excellent yield (Scheme 2). The efficiency of this displacement is certainly enhanced by the high reactivity of the triflate ester, but the rate retardation usually observed in displacements at carbons carrying a β-oxygen substituent does not seem to be as evident in these oxocane hydroxymethyltriflate derivatives as in simpler pyranose compounds, perhaps because of a diminution of the stereoelectronic effect of the oxygen in the eight-membered ring. Attempted displacement of the triflate with the dianion of pentynoic acid[9] was unsuccessful. Completion of the synthesis of the alkynecarboxylic acid **14** was achieved in an analogous manner to that reported in the model series. Our preliminary oxidations of the alkyne **14** to the diketone **2** were again effected with ruthenium tetroxide, but the product was obtained in poor yield and was difficult to characterise. We subsequently discovered that the product was always contaminated with the products of oxidative cleavage of the triple bond, namely succinic acid and the oxocan-2-ylacetic acid.[5] As already reported for the model study ozone was found to be a far superior reagent for this oxidation, and afforded the required *cis*-2,8-disubstituted oxocane **2**.

It was essential also to synthesise the *trans*-isomer **3**, as the methine proton resonances (*e.g.* 13-H as assigned in **1**) in the $^1H$ NMR spectra of *trans*-2,8-disubstituted oxocane derivatives exhibit a downfield trend compared to the corresponding *cis*-compounds. The starting material **15** for the *trans*-isomer **3** is the minor product in the Tebbe methylenation–hydroboration sequence, but reasonable quantities can be obtained by contrathermodynamic epimerisation of the aldehyde (ratio *cis*:*trans* = 6:1) derived from the *cis*-alcohol **11**, followed by sodium borohydride reduction of the equilibrium mixture, and separation of the products.[4a,b] Elaboration of compound **15** to the diketo acid (Scheme 3) followed essentially the same pathway as that already outlined for the synthesis of the *cis*-isomer **2**.

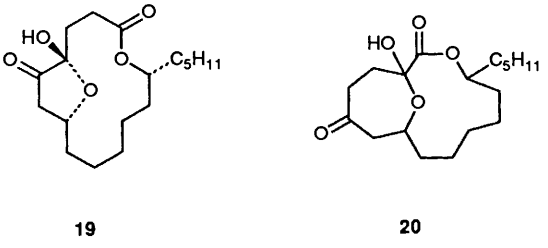
Close examination of the $^1H$ NMR spectra of the isomers **2** and **3** showed no signals (other than OH) at lower field than δ 4.2 (in particular none at δ 5.06), and in the $^{13}C$ NMR spectra only two carbonyl carbon resonances appeared downfield of δ 80 (no signals appearing at δ 99). Thus we concluded that the structure of gloeosporone had been incorrectly assigned. Synthesis of compounds **2** and **3** were described subsequently by two other research groups.[7,8] In contrast to the report of Schreiber[8] we found the ring chain tautomerism of compounds **2** and **3** virtually non existent when we generated the diketone functionality by the ozonolysis route, in agreement with the model study on the preparation of **9**. Our compounds gave clear and unambiguous NMR signals which correlate well with the pure single compounds represented by structures **2** and **3**. The stereochemical assignment is also secure based on the correlation of the *cis*-alcohol **11** with a known degradation product from laurencin.[4a] The spectral data of the compound prepared by Kocienski[7] agree better with our data for the *cis*-compound




**Scheme 3** *Reagents:* i, $Tf_2O$, DMAP, $CH_2Cl_2$, 0 °C (85%); ii, **6**, BuLi, THF, room temperature (84%); iii, TsOH, MeOH, room temperature, 14 h (84%); iv, Jones reagent, ether, room temperature (93%); v, $O_3$, $CH_2Cl_2$, −65 °C (88%); vi, $RuO_2$ (catalytic), $NaIO_4$, $H_2O$, $CCl_4$, MeCN, 0 °C

**2**, rather than the alternative *trans*-isomer **3**. This suggests that the closure of (*E*)-oxacarbenium ions in a Mukaiyama type process[18] is more likely to be *cis*-selective than *trans*-selective in accord with the general mechanistic proposal put forward by Overman for the endocyclic closure of an $sp^2$ centre onto an (*E*)-oxacarbenium ion.[19]

Only two reasonable alternative structures for gloeosporone are consistent with the spectroscopic data. They are both 14-membered lactones, **19** and **20**, thus accounting for the $^1H$ NMR signal at $\delta$ 5.06. The correct structure is **19** as confirmed by X-ray crystallographic analysis[17] and subsequently by total synthesis.[20,8,21,22] In the original structural assignment[2] the concentration-dependent lactone C=O stretching frequency was not detected in the IR spectrum.




We were surprised at the lack of tendency of the diketones **9**, **2** and **3** to cyclise respectively to the lactols **10** and **1**. Calculations at the HF-STO-3G level indicate that the γ-lactol **10** is 34.4 kcal $mol^{-1}$ more stable than the open chain form **9**, and even the six-membered δ-lactol is 30 kcal $mol^{-1}$ more stable than **9**.[23] A survey of the literature revealed that a carbonyl group which is activated by an electron-withdrawing group (*e.g.* $CF_3$ or $CCl_3$) is sufficiently electrophilic to undergo ring chain tautomerism.[24] On the other hand, most α-diketones are not hydrated in aqueous solution;[25] however, those carrying a pendant potential nucleophile may cyclise[26] when special features such as geminal substitution (Thorpe–Ingold effect)[27] or entropic effects are operating.[16,28] It would appear that there is a kinetic barrier to the cyclisation of the α-diketone **9**. It is proposed that the α-diketone is not electrophilic in the s-*trans*-conformation, and becomes much more electrophilic only when it is held in the s-*cis*-conformation, the transition state for nucleophilic attack of which is lower in energy than that for attack on the s-*trans*-conformer.[23] The implication of increased reactivity of the s-*cis*-conformer of an α,β-diketone has also been noted by Bulman Page.[29] *Ab initio* calculations with the 3-21G split-valence basis set suggest that the s-*cis* form is destabilised by at least 5 kcal $mol^{-1}$ compared with the s-*trans*-form, and that there is a correspondence between the ground-state and transition structures.[23] The barrier to *trans–cis* interconversion effectively prevents access to the more electrophilic s-*cis*-form. However, the discrepancy between the very clean spectra of **2** and **3** reported by us in this work, and the data reported by others[7,8] suggest that intramolecular cyclisation can establish an equilibrium between **2** and the cyclic tautomers **1** over time. Also the very existence of the correct structure **19** for gloeosporone evidently indicates that the constraints involved in having the diketone in a medium or large ring sufficiently lower the *trans–cis* energy difference of the α-diketone to allow nucleophilic attack to occur. This hypothesis is supported by molecular mechanics calculations (COSMIC force field).[23] All these issues may play an important part in determining the biological activity of gloeosporone **19**, as noted by Seebach,[20] and may also have wider implications in the relationship between the mode of action of immunosuppressants and their binding to rotamase enzymes.[30]

## Experimental

Apparatus and general experimental procedures have been described in the preceding paper.[4a]

2-(R,S)-(*Pent*-4-*ynyl*-1-*oxy*)*tetrahydropyran* **6**.—Butyllithium (34.4 $cm^3$ of a 1.6 mol $dm^{-3}$ solution in hexane, 0.055 mol) was added dropwise to a stirred solution of ethynyltrimethylsilane (5.4 g, 0.055 mol) in dry THF (150 $cm^3$). After the mixture was stirred for 30 min at room temperature, 2-(*R,S*)-(3-bromopropyloxy)tetrahydropyran **5**[10] (8.1 g, 0.036 mol) and TMEDA (8.3 $cm^3$, 0.055 mol) were added, and the reaction mixture was heated at 60 °C for 18 h. The solution was cooled to 0 °C and TBAF (55 $cm^3$ of a 1 mol $dm^{-3}$ solution in THF, 0.055 mol) was added and the solution was stirred for 30 min. Saturated aqueous ammonium chloride solution (50 $cm^3$) was then added dropwise and the reaction mixture was extracted into diethyl ether (3 × 100 $cm^3$). The organic layer was dried ($MgSO_4$) and

evaporated under reduced pressure to give a residue which was purified by passage through a column of Florisil with 50% dichloromethane in hexane to give the *acetylene* **6** (3.64 g, 60%) as a colourless oil: $\nu_{max}$(neat)/cm$^{-1}$ 3300 (HC≡C), 2940 (CH), 2850 (CH) and 2100 (C≡C); $\delta_H$($CDCl_3$; 250 MHz) 4.57 (1 H, t, *J* 3.8, OCHO), 3.83 (2 H, m, $OCH_AH_B$), 3.60 (2 H, m, $OCH_{A'}H_{B'}$), 2.27 (2 H, dt, *J* 8.2, 2.6, $CH_2C{\equiv}CH$), 1.92 (1 H, t, *J* 2.6, $CH_2C{\equiv}CH$) and 1.84–1.86 (8 H, m, 4 × $CH_2$); $\delta_C$($CDCl_3$; 63 MHz), 98.65 (OCHO), 83.84 and 77.32 (C≡C), 68.37 and 65.63 ($CH_2OCHOCH_2$), 30.54, 28.57, 25.36, 19.39 and 15.22 (5 × $CH_2$).

2-(R,S)-(*Hex*-4-*ynyloxy*)*tetrahydropyran* **7**.—Butyllithium (22.6 cm$^3$ of a 1.6 mol dm$^{-3}$ solution in hexane, 0.042 mol) was added dropwise to a stirred solution of the alkyne **6** (6.5 g, 0.0362 mol) in dry THF (250 cm$^3$) at 0 °C. After 90 min TMEDA (5.85 cm$^3$, 0.0387 mol) was added, followed after 10 min by the dropwise addition of methyl iodide (10 cm$^3$, 0.162 mol). The solution was stirred at 0 °C for 1 h then at room temperature for 14 h. Concentrated aqueous ammonia solution (40 cm$^3$) was added dropwise at 0 °C, and the solution was stirred for 3 h at room temperature. The reaction mixture was extracted into ether (3 × 50 cm$^3$), the organic layer was dried ($MgSO_4$), and evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel, with 50% dichloromethane in hexane as eluent, to give the *hexyne derivative* **7** (5 g, 70%) as a colourless oil (Found: C, 72.7; H, 10.1. $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.95%); $\nu_{max}$(neat)/cm$^{-1}$ 2940 (CH), 2860 (CH) and 1120 (CO); $\delta_H$($CDCl_3$; 250 MHz) 4.59 (1 H, t, *J* 3.6, OCHO), 3.83 (2 H, m, $OCH_AH_B$), 3.46 (2 H, m, $OCH_{A'}H_{B'}$), 2.24 (2 H, m, $CH_3C{\equiv}CCH_2$), 1.76 (3 H, t, *J* 2.2, $CH_3C{\equiv}C$) and 1.86–1.47 (8 H, m, 4 × $CH_2$); $\delta_C$($CDCl_3$; 63 MHz) 98.71 (OCHO), 78.54 and 75.61 (C≡C), 66.07 and 62.07 ($CH_2OCHOCH_2$), 30.65, 29.18, 25.47, 19.47, 15.58 (5 × $CH_2$) and 3.38 ($CH_3C{\equiv}C$); *m*/*z* 181 (M$^+$ − H, 2.5%), 101 (45) and 85 (100).

*Hex*-4-*yn*-1-*ol*.—The THP acetal **7** (2 g, 0.011 mol) was dissolved in dry methanol (50 cm$^3$) with toluene-*p*-sulfonic acid (10 mg) and stirred at room temperature for 16 h. The solvent was removed under reduced pressure to leave a residue which was purified by flash column chromatography on silica gel, with 10% ether in dichloromethane as eluent, to give the *title compound* (1.02 g, 95%) as a colourless oil: $\nu_{max}$(neat)/cm$^{-1}$ 3350 (OH), 2930 (CH) and 2860 (CH); $\delta_H$($CDCl_3$; 250 MHz) 3.74 (2 H, t, *J* 6.2, $CH_2OH$), 2.24 (2 H, m, $CH_3C{\equiv}CCH_2$), 1.77 (3 H, t, *J* 2.6, $CH_3C{\equiv}C$), 1.72 (2 H, m, $CH_2CH_2OH$) and 1.58 (1 H, s, OH); *m*/*z* 98 (M$^+$, 2.65%), 97 (12, M − H), 83 (70, M − $CH_3$), 80 (35, M − $H_2O$) and 79 (100) (Found: M$^+$, 98.0738. $C_6H_{10}O$ requires *M*, 98.0731).

*Hex*-4-*ynoic Acid* **8**.—Hex-4-yn-1-ol **8** (0.9 g, 0.0092 mol) was dissolved in ether (10 cm$^3$) and the solution was added dropwise to a solution of Jones reagent[11] (18.35 cm$^3$ of 2.67 mol dm$^{-3}$, 0.049 mol) at 0 °C. The solution was stirred at room temperature for 30 min, cooled to 0 °C and propan-2-ol (10 cm$^3$) was added dropwise. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between water (50 cm$^3$) and ether (4 × 50 cm$^3$). The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel, with 10% ether in dichloromethane as eluent, to give the *carboxylic acid* **8** (540 mg, 53%) as a colourless solid, m.p. 95–96 °C; $\nu_{max}$(KBr)/cm$^{-1}$ 3500–2400 ($CO_2H$, H-bonding), 2920 (CH) and 1690 (acid C=O); $\delta_H$($CDCl_3$; 250 MHz) 2.53 (2 H, m, $CH_2CO_2H$), 2.44 (2 H, m, $CH_3C{\equiv}CCH_2$) and 1.76 (3 H, t, *J* 2.4, $CH_3C{\equiv}C$); $\delta_C$($CD_3OD$; 63 MHz) 175.90 (C=O), 78.19 and 76.75 (C≡C), 34.84 ($CH_2C{=}O$), 15.44 ($C{\equiv}CCH_2$) and 2.99 ($CH_3C{=}C$); *m*/*z* 112 M$^+$, 3.36%), 111 (11, M − H), 97 (60, M − $CH_3$) and 84 (100).

4,5-*Dioxohexanoic Acid* **9**.—(*a*) *By* $RuO_4$ *oxidation*. The acid **8** (50 mg, 0.446 mmol) was dissolved in acetonitrile (0.5 cm$^3$), carbon tetrachloride (0.5 cm$^3$) and water (0.75 cm$^3$) and cooled to 0 °C. Ruthenium dioxide (2 mg) was added followed by sodium metaperiodate (0.2 g, 0.936 mmol). After the reaction mixture had been stirred for 1 h at 0 °C, starting material was still present (by TLC), therefore more sodium metaperiodate (0.1 g, 0.446 mmol) was added and stirring was continued for a further 30 min. The reaction mixture was filtered through a Celite plug and the solvent was evaporated under reduced pressure to leave a residue which was passed through a column of Florisil, with 10% methanol in dichloromethane as eluent, to give the crude diketo acid **9** (26 mg, 40%) as a viscous green oil which was purified by flash chromatography on silica gel, eluting with ether–hexane–acetic acid (3:6.5:0.5) to give the title compound **9** as yellow crystals, m.p. 76–77 °C (lit.,[17,31] 76–78 °C, 75 °C); $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 3500–2700 ($CO_2H$, H-bonding), 1780w (lactone) and 1710 (1,2-diketone and $CO_2H$); $\lambda_{max}$(EtOH)/nm 407 (ε 25); $\delta_H$($CDCl_3$; 250 MHz) 9.0–7.8 (1 H, br, $CO_2H$), 3.04 (2 H, t, *J* 6.1, $CH_3COCOCH_2$), 2.70 (2 H, t, *J* 6.1, $CH_3COCOCH_2CH_2CO_2H$) and 2.35 (3 H, s, $CH_3CO$-$COCH_2$); $\delta_C$($CDCl_3$; 100.6 MHz) 198.03, 197.77, 178.87, 31.50, 28.36 and 24.64; $\delta_C$($CD_2Cl_2$; 63 MHz; −80 °C) 196.38, 196.23, 179.09, 29.96, 26.64 and 23.69; *m*/*z* 128 (0.23%, M − O), 127 (1.65, M − OH) and 55 (100).

(*b*) *By ozonolysis*. The acid **8** (51.16 mg, 0.453 mmol) was dissolved in methanol (4 cm$^3$) and the solution was cooled to −65 °C. Ozone was passed through the solution and after 1–5 min the reaction turned blue. The cold (−65 °C) reaction mixture was poured into a cold aqueous solution of excess potassium iodide (150 mg, 0.4 mmol) in methanol–acetic acid (1:1 v/v). The resulting mixture was allowed to stand at room temperature for 1 h, after which the liberated iodine was reduced with a solution of aqueous sodium thiosulfate. The colourless reaction mixture was extracted six times with ether, and the combined ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified as above to give the diketo acid **9** (50.3 mg, 77%).

(2S*,8S*)-2-*Pentyl*-8-(*trifluoromethylsulfonyloxy*)*methyloxocane*.—The *cis*-alcohol **11**[4b] (100 mg, 0.468 mmol) and DMAP (0.126 g, 1.03 mmol) were dissolved in dichloromethane (8 cm$^3$) and cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.16 cm$^3$, 1.03 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h, then for 1 h at room temperature. The solvent was then evaporated under reduced pressure and the residue was purified by passage through a column of silica gel (3–4 cm length) with 50% dichloromethane in hexane as eluent to give the *triflate* (133 mg, 83%) as a colourless oil, which was used without further handling.

(2S*,8S*)-2-*Pentyl*-8-[6-(R,S)-*tetrahydropyranyloxyhex*-2-*ynyl*]*oxocane* **12**.—Butyllithium (1.17 cm$^3$ of a 1.6 mol dm$^{-3}$ solution, 1.87 mmol) was added dropwise to a stirred solution of the alkyne **6** (0.346 g, 2 mmol) in dry THF (30 cm$^3$) at room temperature.

After 15 min (2*S**,8*S**)-pentyl-8-(trifluoromethylsulfonyloxy)methyloxocane (106 mg, 0.3063 mmol) dissolved in THF (20 cm$^3$) was added, and the solution was stirred for 6 h (or overnight), then cooled to 0 °C. Saturated aqueous ammonium chloride (15 cm$^3$) was added dropwise and the reaction mixture was extracted into ether (3 × 20 cm$^3$). The ether extracts were washed with brine (2 × 20 cm$^3$), combined, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was heated at 70 °C under vacuum (0.2 mmHg) for 1 h then

purified by flash column chromatography on silica gel with dichloromethane as eluent, to give the *alkyne* **12** (90 mg, 80%) as a colourless oil (Found: C, 75.5; H, 10.9. $C_{23}H_{40}O_3$ requires C, 75.77; H, 11.06%); $\nu_{max}$(neat oil)/cm$^{-1}$ 2940 (CH), 2850 (CH) and 1120 (CO); $\delta_H$($CDCl_3$; 250 MHz), 4.58 (1 H, m, OCHO), 3.82 (2 H, m, $OCHOCH_2$), 3.58–3.40 (4 H, m, $OCHOCH_2$ and $CHOCHCH_2C{\equiv}C$), 2.42–2.16 (4 H, m, $CH_2C{\equiv}CCH_2$), 1.88–1.27 (26 H, m, 13 × $CH_2$) and 0.87 (3 H, t, *J* 6.6, $CH_3$); *m/z* 279 (0.29%, $M^+ - C_5H_9O$ tetrahydropyran), 183, (2, $M - CH_2C{\equiv}CCH_2CH_2CH_2OTHP$) and 85 (100).

(2S*,8S*)-2-(6-*Hydroxyhex*-2-*ynyl*)-8-*pentyloxocane* **13**.—The THP acetal **12** (65 mg, 0.178 mmol) was dissolved in dry methanol (15 cm$^3$) with toluene-*p*-sulfonic acid (1 mg) and the solution was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, with 20% diethyl ether in dichloromethane as eluent, to give the *alcohol* **13** (47.4 mg, 95%) as a colourless oil (Found: C, 77.0; H, 11.7. $C_{18}H_{32}O_2$ requires C, 77.09; H, 11.50%); $\nu_{max}$(neat)/cm$^{-1}$ 3400 (OH), 2940 (CH), 2850 (CH) and 1080 (C–O); $\delta_H$($CDCl_3$; 250 MHz) 3.74 (2 H, t, *J* 6.1, $HOCH_2$), 3.58 (1 H, m, $CHOCHCH_2C{\equiv}C$), 3.46 (1 H, m, $CHOCHCH_2C{\equiv}C$), 2.39–2.16 (4 H, m, $CH_2C{\equiv}CCH_2$), 1.83–1.27 (21 H, m, 10 × $CH_2$ and OH) and 0.87 (3 H, t, *J* 6.7, $CH_3$); $\delta_C$($CDCl_3$, 63 MHz) 80.45 and 78.86 (*C*HOCH), 80.37 and 78.54 (C≡C), 62.02 ($CH_2OH$), 36.90, 33.91, 33.08, 32.00, 31.62, 27.16, 26.68, 25.98, 24.43, 24.38, 22.64, 15.53 and 14.02 ($CH_2C{\equiv}CCH_2$), 10 × $CH_2$ and 1 × $CH_3$); *m/z* 183 [37%, $M^+ - CH_2C{\equiv}C(CH_2)_3OH$] and 95 (100).

(2S*,8S*)-2-(5-*Carboxypent*-2-*ynyl*)-8-*pentyloxocane* **14**.—The alcohol **13** (38 mg, 0.135 mmol) was dissolved in dry dichloromethane (3 cm$^3$) and dry powdered 3Å molecular sieves (200 mg) were added. PCC (58.2 mg, 0.27 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. Ether (20 cm$^3$) was added and the solution was filtered through a column of Florisil with 3 column volumes of ether. The solvents were evaporated under reduced pressure to give the crude aldehyde as a colourless oil which was redissolved in ether (1.5 cm$^3$) and oxidised with Jones reagent[11] (0.11 cm$^3$, 2.67 mol dm$^{-3}$). The reaction mixture was stirred at room temperature for 1 h then saturated aqueous sodium hydrogen carbonate solution (5 cm$^3$) was added dropwise at 0 °C. Hydrochloric acid (1 mol dm$^{-3}$) was added dropwise to adjust the mixture to pH 1 and the reaction mixture was extracted with ether (4 × 10 cm$^3$), dried ($MgSO_4$) and evaporated under reduced pressure. The resultant residue was purified by flash column chromatography on silica gel, with 50% ether in dichloromethane as eluent, to give the *carboxylic acid* **14** (33.5 mg, 84%) as a viscous colourless oil; $\nu_{max}$(neat)/cm$^{-1}$ 3500–2400 ($CO_2H$, H-bonding), 2940 (CH), 2850 (CH), 1705 (acid C=O) and 1100 (CO); $\delta_H$($CDCl_3$; 250 MHz) 3.57 (1 H, m, $OCH$-$CH_2C{\equiv}C$), 3.45 (1 H, m, $CHOCHCH_2C{\equiv}C$), 2.60–2.42 (4 H, m, $C{\equiv}CCH_2CH_2CO_2H$), 2.38 (1 H, dd, *J* 16.4, 6.3, $OCH$-$CH_AH_BC{\equiv}C$), 2.20 (1 H, dd, *J* 16.4, 7.0, $OCHCH_AH_BC{\equiv}C$), 1.87–1.17 (18 H, m, 9 × $CH_2$) and 0.87 (3 H, t, *J* 6.6, $CH_3$); $\delta_C$($CDCl_3$; 63 MHz) 177.08 (C=O), 80.49 and 78.8 (*C*HOC*H*), 79.00 and 77.50 (C≡C), 36.89, 33.88, 33.64, 33.03, 32.00, 27.13, 26.63, 26.00, 24.39 (2 C), 22.66, 14.58, 14.05 (12 × $CH_2$ and 1 × $CH_3$); *m/z* 183 (3.11% $M^+ - CH_2C{\equiv}CCH_2CH_2CO_2H$) and 55 (100).

(2S*,8S*)-2-(5-*Carboxy*-2,3-*dioxopentyl*)-8-*pentyloxocane* (cis-pseudo-*Gloeosporone*) **2**.—The alkyne **14** (28.68 mg, 0.097 mmol) was dissolved in dry dichloromethane (4 cm$^3$). The solution was then cooled to −65 °C and ozone was passed through the stirred solution for 15 min. Oxygen was then passed through the solution for 10 min, followed by argon (10 min). The solution was then allowed to warm to room temperature and poured into an ice cold mixture of acetic acid (2 cm$^3$), methanol (2 cm$^3$) and potassium iodide (90 mg, 0.54 mmol). The mixture was stirred for 1 h and then a solution of aqueous sodium thiosulfate was added dropwise, until the colour due to liberated iodine disappeared. The reaction mixture was extracted with dichloromethane (50 cm$^3$) and then ether (5 × 50 cm$^3$) and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by flash column chromatography on silica gel, using ether–hexane–acetic acid (3:6.5:0.5) as the eluent to give the *diketone* (cis-pseudo-*gloeosporone*) **2** (31.72 mg, 100%) as a yellow oil; $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 3300–3000, 2920, 2860, 1780, 1725, 1715, 1345, 1130 and 1085; $\delta_H$($CDCl_3$; 400 MHz) 3.98 (1 H, m), 3.41 (1 H, m), 3.06 (1 H, dd, *J* 15.3, 8.8), 2.70–2.96 (2 H, m), 2.47–2.70 (3 H, m), 1.97 (1 H, s), 1.17–1.70 (18 H, m) and 0.81 (3 H, t, *J* 6.8); $\delta_C$($CDCl_3$; 100.6 MHz) 198.8, 177.5, 79.8, 75.5, 43.1, 36.6, 33.3, 33.3, 31.9, 29.7, 27.8, 26.6, 25.7, 23.6, 23.6, 23.6, 22.6 and 14.0; *m/z* 326 ($M^+$, 11.7%) (Found: $M^+$, 326.2082. $C_{18}H_{30}O_5$ requires *M*, 326.2093).

(2S*,8R*)-2-*Pentyl*-8-(*trifluoromethylsulfonyloxymethyl*)-*oxocane*.—The *trans*-alcohol **15**[4b] (84.80 mg, 0.396 mmol) and 4-dimethylaminopyridine (106 mg, 0.87 mmol) were dissolved in dry dichloromethane (6 cm$^3$) and cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.133 cm$^3$, 0.791 mmol) was then added dropwise and the reaction mixture was stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the product was purified by flash column chromatography using a short column of silica and eluting with hexane–dichloromethane (1:1). The solvent was then removed under reduced pressure to give the *title compound* (117 mg, 85%) as a colourless liquid which was used without further handling.

(2S*,8R*)-2-*Pentyl*-8-[6-(R,S)-(*tetrahydropyranyloxy*)-*hex*-2-*ynyl*]*oxocane* **16**.—2-(R,S)-Pent-4-ynyl-1-oxytetrahydropyran **6** (399 mg, 1.98 mmol) was dissolved in dry THF (25 cm$^3$) and butyllithium (1.11 cm$^3$ of a 1.6 mol dm$^{-3}$ solution in hexanes, 1.78 mmol) was added. The reaction was then stirred at room temperature for 20 min before the triflate ester of the alcohol **15** (117 mg), dissolved in dry THF (10 cm$^3$), was added. After addition of the triflate, the reaction was stirred at room temperature for 16 h. After this time a solution of saturated aqueous ammonium chloride (10 cm$^3$) was added to the solution at 0 °C. The aqueous layer was then extracted with ether (3 × 50 cm$^3$) and the combined organic extracts were washed with water (20 cm$^3$) then brine (20 cm$^3$). The extracts were then dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was heated to 70 °C under high vacuum for 1 h. The product was then purified by flash column chromatography on silica gel, eluting with dichloromethane, to afford the *alkyne* **16** (103.74 mg, 84%), as a colourless liquid. This alkyne was carried through to the next stage without further characterisation.

(2R*,8S*)-2-(6-*Hydroxyhex*-2-*ynyl*)-8-*pentyloxocane* **17**.—The THP-acetal **16** (103.74 mg, 0.285 mmol) was dissolved in dry methanol (25 cm$^3$) and toluene-*p*-sulfonic acid (5 mg) was added. The reaction was then stirred at room temperature for 16 h. After this time, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with hexane–ethyl acetate (4:1), to give the *alcohol* **17** (74.22 mg, 93%; $\nu_{max}$($CHCl_3$)/cm$^{-1}$ 3620 (OH), 2930 (CH), 2860 (CH), 2250 (C≡C) and 1070 (CO); $\delta_H$($CDCl_3$; 250 MHz) 3.73 (2 H, t, *J* 6.1, $CH_2OH$), 3.80–3.69 (2 H, m, $CHOCHCH_2C{\equiv}C$), 2.36–2.15 (4 H, m, $CH_2C{\equiv}CCH_2$), 1.77–1.19 (21 H, m, 10 × $CH_2$ and OH) and 0.87 (3 H, t, *J* 6.5, $CH_3$); $\delta_C$($CDCl_3$; 63 MHz) 80.97 and 78.27 (C≡C), 75.84, and

72.01 (CHOCH), 62.09 ($CH_2OH$), 36.26, 32.60, 32.04 (2 C), 31.61, 27.39, 26.40, 26.26, 25.96, 25.40, 22.66, 15.60, 14.02 (12 × $CH_2$ and 1 × $CH_3$); *m/z* 280 ($M^+$, 0.9%), 209 (1, M − $C_5H_{11}$), 183 (35, M − $CH_2C{\equiv}C(CH_2)_3OH$) and 95 (100) (Found: $M^+$, 280.2407. $C_{18}H_{32}O_2$ requires *M*, 280.2402).

(2R*,8S*)-2-(5-*Carboxypent*-2-*ynyl*)-8-*pentyloxocane* **18**.—The alcohol **17** (74.22 mg, 0.265 mmol) was dissolved in ether (26 $cm^3$) and Jones reagent[11] (0.22 $cm^3$ of 2.67 mol $dm^{-3}$ solution, 0.59 mmol) was added. The reaction was stirred for 2 h. After this time the reaction was judged to have gone less than half way, so more Jones reagent (1.0 $cm^3$, 2.67 mmol) was added. The reaction was complete in 15 min. The reaction pH was adjusted to pH 7 by addition of saturated aqueous sodium hydrogen carbonate, then reacidified to pH 1 with hydrochloric acid (2 mol $dm^{-3}$). The reaction mixture was then extracted with ether (4 × 100 $cm^3$) and the organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with dichloromethane–ether (1:1) to give the *carboxylic acid* **18** (61.81 mg, 79% yield), as a viscous colourless liquid; $\nu_{max}(CHCl_3)/cm^{-1}$ 3400–2300 ($CO_2H$, H-bonding), 2930 (CH), 2840 (CH), 1710 (acid C=O) and 1070 (CO); $\delta_H(CDCl_3$; 250 MHz) 3.78 (1 H, m, C*H*OCHCH$_2$C≡C), 3.62 (1 H, m, CHOC*H*CH$_2$C≡C), 2.60–2.43 (4 H, m, C≡CC*H*$_2$C*H*$_2$CO$_2$H), 2.30 (1 H, ddd, *J* 15.4, 5.4, 2.3, OCHC*H*$_A$*H*$_B$C≡C), 2.21 (1 H, ddd, *J* 15.4, 7.3, 2.3, OCHCH$_A$*H*$_B$C≡C), 1.75–1.25 (18 H, m, 9 × $CH_2$) and 0.88 (3 H, t, *J* 6.5, $CH_3$); $\delta_C(CDCl_3$; 63 MHz) 176.46 (acid C=O), 79.45, and 78.73 (C≡C), 75.84 and 72.09 (CHOCH), 36.30, 33.60, 32.51, 32.10, 32.06, 27.36, 27.43, 26.25, 25.97, 25.44, 22.68, 14.68, 14.02 (12 × $CH_2$ and 1 × $CH_3$); *m/z* 223 (1% $M^+$ − $C_5H_{11}$), 183 (7, M − $CH_2C{\equiv}CCH_2CH_2CO_2H$) and 55 (100).

(2R*,8S*)-2-(5-*Carboxy*-2,3-*dioxopentyl*)-8-*pentyloxocane* (trans-pseudo-*Gloeosporone*) **3**.—The alkyne carboxylic acid **18** (61.81 mg, 0.210 mmol) was dissolved in dry dichloromethane (4 $cm^3$). The solution was then cooled to −65 °C and ozone was passed through the stirred solution for 10 min. Oxygen was then passed through the solution for 10 min, followed by argon (5 min). The solution was then allowed to warm to room temperature and poured into an ice cold mixture of acetic acid (3 $cm^3$), methanol (3 $cm^3$) and potassium iodide (190 mg, 1.14 mmol). The mixture was stirred for 1 h and then a solution of aqueous sodium thiosulfate was added dropwise, until the colour due to liberated iodine disappeared. The reaction mixture was then extracted with dichloromethane (50 $cm^3$) and then ether (5 × 50 $cm^3$) and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the product was purified by flash column chromatography on silica gel, using ether–hexane–acetic acid (3:6.5:0.5) as the eluent. The *diketone* (trans-pseudo-*gloeosporone*) **3** (60.52 mg, 88%) was obtained as a yellow liquid; $\nu_{max}(CHCl_3)/cm^{-1}$ 3500–3000, 2930, 2855, 1790, 1725, 1715 and 1075; $\lambda_{max}$(EtOH) 260 nm (ε 343), 417 (18); $\delta_H(CDCl_3$; 400 MHz) 4.16 (1 H, m), 3.57 (1 H, m), 2.86 (3 H, m), 2.75 (1 H, dd, *J* 15.5, 5.9), 2.62 (2 H, t, *J* 6.3), 2.03 (1 H, s), 1.13–1.59 (18 H, m) and 0.81 (3 H, t, *J* 6.9); $\delta_C(CDCl_3$; 100.6 MHz) 197.9, 177.5, 75.7, 69.7, 43.7, 36.0, 33.3, 31.8, 31.8, 30.6, 27.5, 26.2, 25.8, 25.8, 25.2, 22.6 and 14.0; *m/z* 326 ($M^+$, 1.6%) (Found: $M^+$, 326.2104. $C_{18}H_{30}O_5$ requires *M*, 326.2093).

## Acknowledgements

We thank the SERC for supporting this work and the D.A.A.D. and St Catharine's College, Cambridge for the award of a studentship (D. S.). We thank Professors W. L. Meyer, D. Seebach and S. L. Schreiber for information and spectra of gloeosporone and *pseudo*-gloeosporone, Drs. D. J. Chadwick and J. K. M. Sanders for helpful discussions, and Drs. T. A. Carpenter, S. Naylor and J. Waltho for NMR spectra. We thank Professor S. D. Kahn for numerous stimulating discussions on the computational work, which he performed in part with Dr. N. C. Handy and Mr. P. J. Agg,[23] and Merck, Sharp & Dohme (Harlow) for support with provision of computer modelling facilities.

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*Paper* 1/03824I
*Received* 25*th July* 1991
*Accepted* 23*rd September* 1991