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Synthetic study of phomoidride B (CP-263,114); utilization of the oxidopyrylium [5 + 2] cycloaddition

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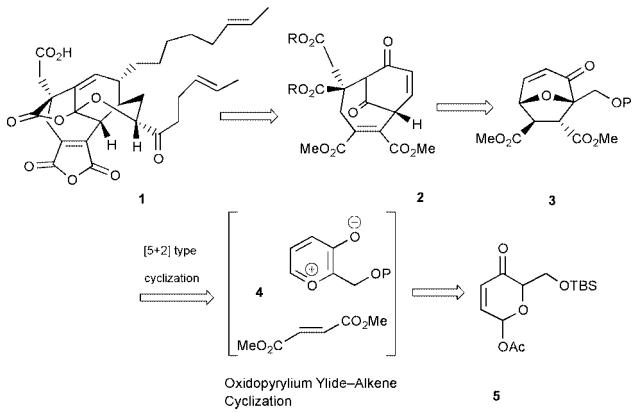
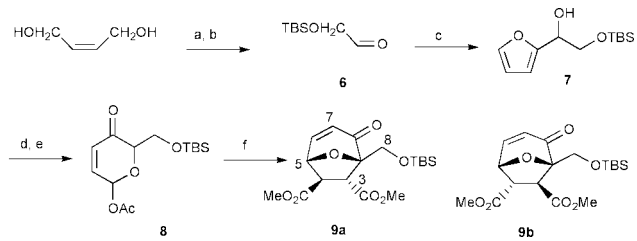
The highly functionalized core structure of phomoidride B (CP-263,114) was pursued by using intermolecular oxidopyrylium–alkene cyclization as one of the key steps.

In 1997, the group of Kaneko reported the structure of phomoidride B (**1**) and its hydrolysed derivatives, both showing inhibitory activity towards farnesyl transferase[1] with IC_{50} values in the micromolar range.[2] A great many synthetic organic chemists have been attracted by its fascinating structural features and so far four groups have achieved elegant complete total syntheses.[3] Retrosynthetic analysis suggested that **1** could be accessed from **2** by introducing side chains followed by minimal functional group manipulations. Bicyclic **2** in turn could be constructed from modestly functionalized seven-membered ring **3**, which could easily be obtained by treating the oxidopyrylium ylide[4] **4** with fumarate ester or its variants thus providing easy access to the maleic anhydride moiety of the CP-core (Scheme 1).

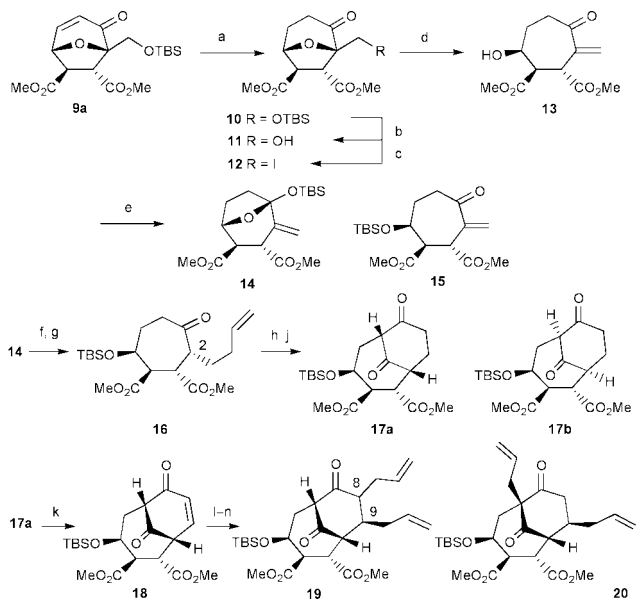


Scheme 1 Strategy for the total synthesis of phomoidride B (**1**).

The synthesis began with the protection of but-2-ene-1,4-diol with TBSCl (Scheme 2). Oxidopyrylium precursor **8** was easily prepared in 5 steps (39% from but-2-ene-1,4-diol). When using dimethyl fumarate as the alkene, cyclization took place quite efficiently in the presence of Et_3N to deliver oxabicycles **9a** and **9b** (13 : 1) in 77% combined yield. Hydrogenation of **9a** followed by the removal of the silyl protecting group and iodination gave **12** (Scheme 3). Of several attempts to cleave the ether bridge in reductive fashion, Zn proved to be the most suitable, yielding *exo*-enone **13** in 96% yield. Homologation of the *exo* olefin seemed reasonable for introducing the lacking two carbon unit required for construction of the bicyclo-[4.3.1]decene core. To this end, **13** was treated with TBSOTf in the presence of 2,6-lutidine to give a separable mixture of TBS-protected acetal **14** (49%) and enone **15** (5%). Acetal **14** was next converted to **16**† in two steps by allylation in the presence of $TiCl_4$ followed by reprotection of the liberated alcohol with TBSOTf. Ketone **16** was subjected to ozonolysis to yield a keto-aldehyde, which was subsequently treated with DBU to promote the intramolecular aldol reaction.[6] The crude aldol adduct was oxidized with PCC to deliver diketones **17a** and **17b** (4 : 1, 82% yield over 2 steps). Oxidation of **17a** to enone **18** under Saegusa's conditions[7] proceeded in 35% yield. Improved yields were obtained using the recently reported Nicolaou method using IBX (IBX = 2-iodylbenzoic acid),[8] giving enone **18** in 30% yield along with recovery of the starting material (42%). Repeated oxidation of recovered **17a** resulted in a combined yield of 42% (52%, based on recovered **17a**). Lewis acid catalyzed allylation of **18** gave a 1,4-adduct as a single stereoisomer. Further allylation utilizing palladium chemistry



Scheme 2 *Reagents and conditions*: (a) TBSCl, Et_3N, DMAP, THF, rt; (b) O_3, MeOH, −78 °C, then $NaHCO_3$, Me_2S, −78 °C → rt, quant. (2 steps); (c) 2-lithiofuran, Et_2O, −78 °C → rt; (d) MCPBA, CH_2Cl_2, 0 °C → rt; (e) Ac_2O, pyridine, rt, 39% (3 steps); (f) dimethyl fumarate, Et_3N, CH_3CN, reflux, 77% (**9a** : **9b**, 13 : 1).



Scheme 3 *Reagents and conditions*: (a) H_2, Pd/C, MeOH, rt; (b) aq. HCl, rt; (c) I_2, PPh_3, imidazole, benzene, reflux, 64% (3 steps); (d) Zn, MeOH, reflux, 96%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 54% (**14** : **15**, 10 : 1); (f) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C; (g) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 66% (2 steps); (h) O_3, MeOH, then $NaHCO_3$, Me_2S, −78 °C → rt, 81%; (i) DBU, CH_2Cl_2; (j) PCC, CH_2Cl_2, 4 Å MS, rt, 82% (2 steps, **17a** : **17b**, 4 : 1); (k) IBX, DMSO–PhMe (1 : 2), 80 °C, 52%; (l) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78 °C, 57%; (m) KHMDS, allyl chloroformate, THF, −78 °C, 63%; (n) $Pd_2(dba)_3$·$CHCl_3$, PPh_3, THF, rt, 81% (**19** : **20**, 2 : 1).

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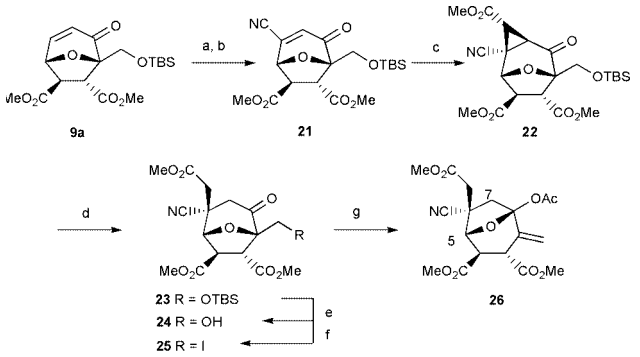

Scheme 4 *Reagents and conditions*: (a) Br_2, CH_2Cl_2, −40 °C, then Et_3N, −40 °C → rt; 99%; (b) NaCN, Bu_4NI, CH_2Cl_2—H_2O, rt, then Et_3N, rt, 97%; (c) $Me_2S{=}CHCO_2Me$, THF, 0 °C → rt, 61%; (d) SmI_2, THF, −78 °C, 79%; (e) aq. HCl, 0 °C → rt; (f) I_2, PPh_3, imidazole, benzene, reflux, 64% (2 steps); (g) Zn, Ac_2O, 50 °C, 25%.

delivered **19**‡ (19% yield from **18**) a highly advanced bicyclic intermediate with the required relative stereochemistry between the bridging carbonyl group and the hydrophobic side-chain at C9 along with **20** (10% yield from **18**).

Having established a method for the construction of the bicyclic framework, we then focussed upon the quaternary carbon centre adjacent to the bridgehead. To this end **9a** was first converted to **21** in 2 steps (96%) (Scheme 4). Various attempts to produce directly the desired quaternary centre with organometal reagents were unsuccessful, probably due to the highly functionalized nature of **21**. Only by using a sulfonium ylide did the reaction take place without any problems, furnishing a cyclopropane product **22**. Reductive cleavage of **22** with SmI_2 proceeded with complete regioselectivity to generate the required quaternary centre.§ Compound **23** was next deprotected under acidic conditions followed by iodination to give **25**. Zinc reduction and protection of the resultant hydroxy group with an acetyl group gave **26**.¶

We are currently exploring methods to complete the fully functionalized core and modify the side chains *en route* to phomoidride B.

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Notes and references

† In this reaction **16** was obtained stereoselectively at the C2 centre. While the reason for this selectivity is unclear, it may be due to the proton delivering effect of the hydroxy group in the intermediate silyl enol ether during work-up (ref. 5).

‡ Although the C8 stereochemistry of **19** is not certain, **19** was obtained as the sole stereoisomer.

§ Although SmI_2 has previously been used for cyclopropane opening (ref. 10), to our knowledge, regioselective opening of cyclopropane bearing electron stabilizing groups on all three carbons with SmI_2 is unprecedented.

¶ *Data* for **9a**: R_f = 0.39 (silica gel, EtOAc–hexane 1:2); mp 92–94 °C (CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2955, 1740, 1695; δ_H (500 MHz, $CDCl_3$) 7.34 (dd, *J* 9.8, 4.6, 1H, H-6), 6.02 (d, *J* 9.8, 1H, H-7), 5.19 (d, *J* 4.6, 1H, H-5), 4.25 (d, *J* 11.9, 1H, H-8), 4.22 (d, *J* 4.3, 1H, C*H*CO_2Me), 4.01 (d, *J* 11.9, 1H, H-8), 3.76 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3), 3.61 (d, *J* 4.3, 1H, C*H*CO_2Me), 0.90 (s, 9H, Si-*t*-*Bu*), 0.11 (s, 3H, Si-*Me*) 0.70 (s, 3H, Si-*Me*); δ_C (125 MHz, $CDCl_3$) 193.6, 171.0, 170.3, 150.7, 127.3, 91.7, 75.9, 60.3, 52.6, 52.4, 50.6, 46.6, 25.6, 18.1, −5.5, −5.7. HRMS (EI): calc. for $C_{18}H_{28}O_7Si$ (M^+): 384.1604. Found: 384.1588. Anal calc: C 56.23, H 7.34. Found: C 56.13, H 7.43%. For **26**: R_f = 0.53 (silica gel, EtOAc–hexane 1:1); ν_{max}(neat)/cm^{-1} 2955, 1740, 1440; δ_H (500 MHz, $CDCl_3$) 5.59 (br s, 1H, *exo*-CH_2=), 5.09 (s, 1H, *exo*-CH_2=), 4.99 (s, 1H, H-5), 4.23 (d, *J* 7.0, 1H, C*H*CO_2Me), 3.81 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CO_2CH_3), 3.77 (s, 3H, CO_2CH_3), 3.66 (dd, *J* 7.0, 1.8, 1H, C*H*CO_2Me), 3.08 (d, *J* 17.4, 1H, CH_2CO_2Me), 3.00 (d, *J* 17.4, 1H, CH_2CO_2Me), 2.89 (d, *J* 13.7, 1H, H-7), 2.62 (d, *J* 13.7, 1H, H-7), 2.11 (s, 3H, acetyl); δ_C (125 MHz, $CDCl_3$) 171.8, 171.5, 169.4, 167.6, 141.4, 119.8, 113.3, 104.9, 80.9, 53.1, 52.8, 52.3, 45.9, 45.5, 44.6, 43.1, 40.9, 21.6. HRMS (EI) calc. for $C_{18}H_{21}O_9Si$ (M^+): 395.1216. Found: 395.1212.

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