Synthesis of the Oxygenated Bicyclo[9.3.1]pentadecane Ring System of Phomactin A using Chromium (II)-mediated Macrocyclisation and Ring Closure Metathesis

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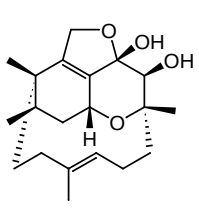
Abstract: Treatment of the aldehyde vinyl iodides **17**, **19a** and **19b** in DMSO with $CrCl_2$-$NiCl_2$ resulted in their macrocyclisation to the oxygenated ring systems **18**, **20**, and **21** respectively (43-63%) of the PAF antagonist phomactin A isolated from the marine fungus *Phoma sp.* The same bicyclo[9.3.1]pentadecane ring system **24** could also be produced by treatment of the polyene **23** with Grubbs' ruthenium catalyst in hot CH_2Cl_2 for 10 h (~30%).

Key words: macrocyclisation, chromium (II), phomactin A, metathesis, PAF

Phomactin A (**1**) is a novel oxygenated diterpene isolated from the marine fungus *Phoma sp*,[1] and is a specific platelet activating factor (PAF)-antagonist.[2,3] The natural product has a unique structure which features an unusual furanochroman ring system **2** making up part of a macrocyclic bicyclo[9.3.1]pentadecane core **3**. This novel structure, alongside its biogenetic relationship with the taxane ring system,[4] and its interesting PAF-antagonist activity, combine to make phomactin A and its congeners extremely attractive targets for total synthesis and for biological evaluation. In an earlier publication[5] we described a concise synthesis of the tricyclic furanochroman unit **2** found in phomactin A.[6] In this communication we outline a synthesis of the oxy-substituted bicyclo[9.3.1]pentadecatriene **3** containing all the carbon atoms and most of the oxygen centres in this intriguing natural product.[7]



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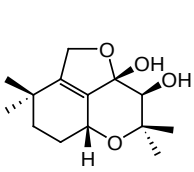

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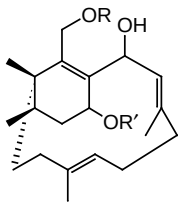


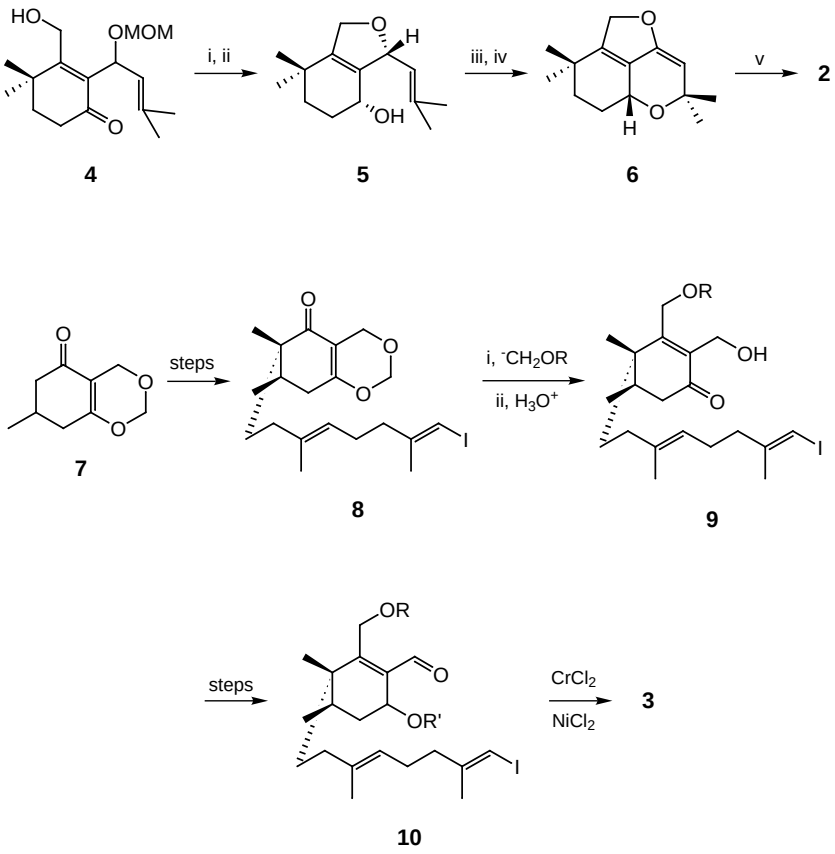
3

In our earlier published synthesis of the model furanochroman **2**, a key intermediate was the corresponding hydroxymethyl substituted cyclohexenone **4** which was elaborated to **2** in five steps via the dihydrofuran **5** and the tricyclic enol ether **6** as key intermediates (Scheme 1).[5]

Our strategy for achieving a total synthesis of phomactin A itself, therefore, was based on elaborating the substituted bicyclo[9.3.1]pentadecane **3** and then completing the synthesis via similar intermediates to those used in the conversion of **4** into **2**. Although a wide range of macrocyclisation protocols were examined to synthesise the macrocyclic core in structure **3**, the method we describe here is based on an intramolecular Cr(II) mediated coupling reaction from the aldehyde vinyl iodide intermediate **10** [the so-called Nozaki-Hiyama-Kishi (NHK) reaction].[8] In turn, we planned to synthesise this pivotal intermediate **10** from the readily available dioxin **7**[9] and proceeding via an alkylation reaction sequence, leading to **8**, followed by introduction of the hydroxymethyl functionality, producing **9** and, finally, manipulation of the functionality in **9** (Scheme 1).

Thus, sequential deprotonation and alkylation of the dioxin **7** derived from 5-methylcyclohexane 1,3-dione using, firstly LDA and MeI, and then LDA and the *E*,*E*-iododiene **14**, produced the substituted dioxin **8** as a 3:1 mixture of diastereoisomers in favour of the *syn*-dimethyl diastereoisomer shown. The homoallylic iodide **14** was synthesised by way of a palladium catalysed cross-coupling reaction between the homopropargylic iodide **11** and the *E*-vinyl iodide **12**,[10] leading to **13**, followed by desilylation and a zirconium assisted carboalumination-iodination[11] process as key steps (Scheme 2).

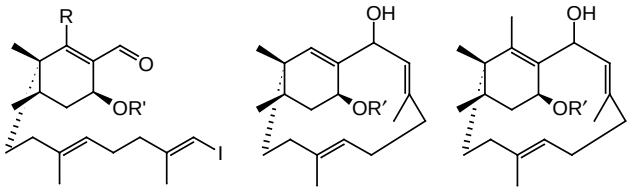
1,2-Addition of *p*-methoxybenzylmethyl lithium[12] to the vinylogous ether **8** followed by work-up with dilute HCl next led to the corresponding enone **15** in a modest 43% yield over two steps. Protection of the alcohol group in **15** and reduction of the carbonyl function, under Luche conditions,[13] then led to the corresponding β-orientated secondary alcohol which was protected as its MOM ether **16**. Finally, saponification of **16** followed by oxidation of the resulting primary alcohol using Dess-Martin periodinane,[14] led to the key aldehyde vinyl iodide **17** (*cf* **10**). Treatment of a solution of the aldehyde vinyl iodide **17** in DMSO with 6 equivalents of $CrCl_2$ and 0.25 equivalents of $NiCl_2$ resulted in smooth macrocyclisation and the formation of the macrocyclic secondary alcohol **18** as a 1:1 mixture of α- and β-OH epimers in a combined yield of 52%.[15] The structures and stereochemistries of the intermediate **16** and the product **18** produced in this sequence followed from comparison of spectroscopic data with the more simple analogues **20** and **21** synthesised by an iden-



Reagents: i,CSA, CH_2Cl_2, RT, 91%; ii, $^iBu_2AlH$, PhMe, -78 °C, 46%; iii, PhSeBr, Et_3N, CH_2Cl_2, -78 °C, 77%; iv, m-CPBA, CH_2Cl_2, 0 °C; KOH, THF, Δ; v, DMDO, Me_2CO, H_2O, 0 °C, 22% (3 steps).

Scheme 1

tical strategy. The structure and stereochemistry of the crystalline alcohol **20** produced via a NHK reaction from **19a** was established by X-ray crystal structure analysis,[16] whereas the structure and stereochemistry of **21**, obtained from **19b**, was secured from NOE experiments in its NMR spectrum and from complementary molecular modelling data.



19
a R = H
b R = Me

20 R′ = MOM **21** R′ = MOM

We have therefore accomplished, for the first time, a synthesis of the phomactin A ring system containing all the carbon atoms and all the necessary oxygen centres in readiness for elaboration to the target natural product itself. In complementary synthetic studies we also synthesised the ring closure metathesis precursor **23** starting from the substituted 3-ethoxy-cyclohex-2-enone **22** and using methods similar to those used to produce precursors to **17** and **19** from **7** (Scheme 3).[17] When a refluxing solution of the polyene **23** in CH_2Cl_2 was exposed to Grubbs' ruthenium catalyst[18] (30 mol%) for 10 h, the corresponding macrocyclic polyene **24** was isolated in an unoptimised 27% yield with exclusively the *E*-geometry at the newly introduced alkene bond. Further studies are now underway in our laboratories to develop the strategies described here towards bicyclo[9.3.1]pentadecanes, en route to phomactin A (**1**) and other biologically important phomactinoids. These studies will be described in due course.

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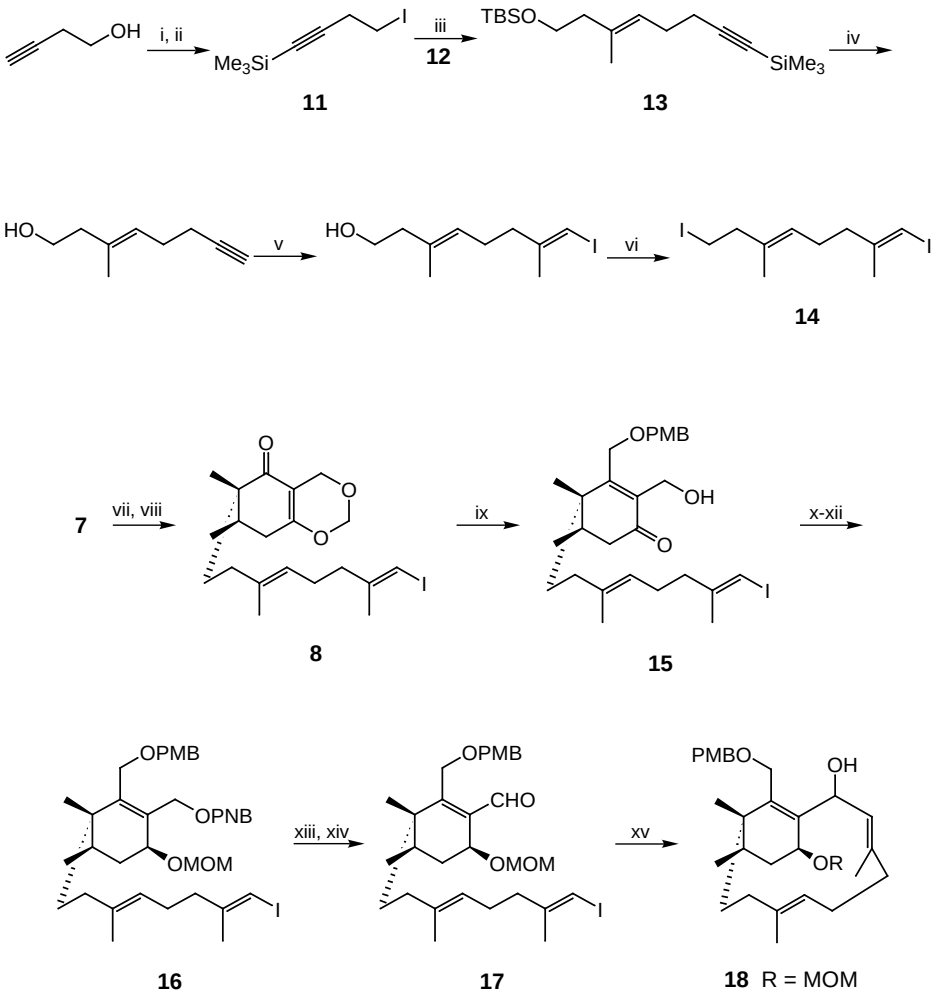

Reagents: i, BuLi, TMSCl, THF, -78 → 0 °C, then HCl, Et_2O, 94%; ii, I_2, PPh_3, Imidazole, Et_2O-CH_3CN (3:1), 92%; iii, ^tBuLi, $ZnCl_2$, THF, -78 °C; then $Pd(PPh_3)_4$, *(E)*-$TBSOCH_2CH_2(CH_3)C{=}CHI$ (**12**); iv, TBAF, THF, 87% (2 steps); v, $AlMe_3$, Cp_2ZrCl_2, CH_2Cl_2; then I_2, THF, 83%; vi, I_2, PPh_3, Imidazole, Et_2O-CH_3CN (3:1), 96%; vii, LDA, THF, -78 °C; then MeI, 96%; viii, LDA, THF, -78 °C; then **14**, 76%; ix, $PMBOCH_2SnMe_3$, BuLi, Et_2O, -78 °C; then HCl, THF, 43%; x, *p*-$NO_2C_6H_4COCl$, Et_3N, DMAP, CH_2Cl_2, 92%; xi, $NaBH_4$, $CeCl_3{\bullet}7H_2O$, MeOH, CH_2Cl_2, 83%; xii, MOM-Cl, $^iPr_2EtN$, Bu_4NI, CH_2Cl_2; xiii, KOH, MeOH, 87% (2 steps); xiv, Dess-Martin periodinane, C_5H_5N, CH_2Cl_2, 0 °C, 98%; xv,$CrCl_2$ (6 eq.), $NiCl_2$ (0.25 eq.), DMSO, 52%.

Scheme 2

References and Notes

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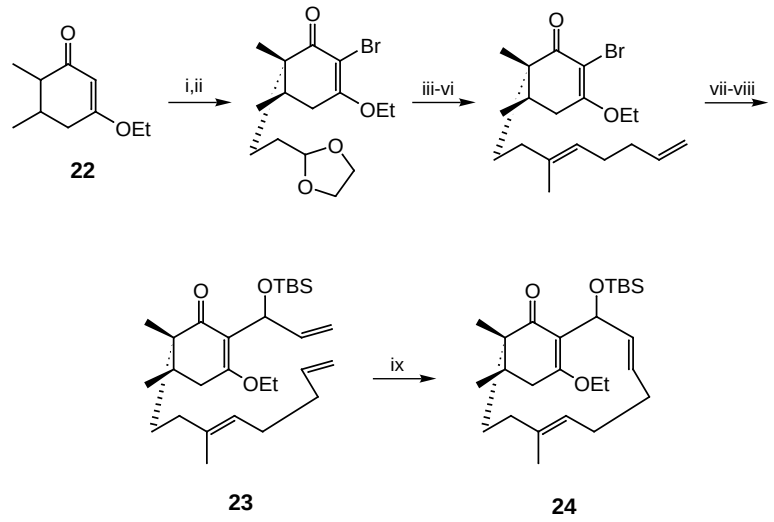

Reagents: i, LDA, THF, -78 °C, then $ICH_2CH_2CH(OCH_2CH_2O)$, 70%; ii, NBS, CCl_4, 25 °C, 68%; iii, $PdCl_2(MeCN)_2$, Me_2CO, 75%; iv, MeMgCl, THF, 0 °C, 66%; v, Dess-Martin periodinane, CH_2Cl_2, 0 °C, 99%; vi, $H_2C{:}CHCH_2CH_2CH_2PPh_3Br$, BuLi, Et_2O, -78 °C, 58%; vii, ^{t}BuLi, THF, -78 °C, then $CH_2{=}CHCHO$, 76%; viii, TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 86%; ix, $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, Δ, 10 h, 27%.

Scheme 3

(15) All new compounds showed satisfactory spectroscopic and analytical data. Typical procedure for the preparation of **18**: A mixture of chromium dichloride (23 mg, 0.226 mmol) and nickel chloride (1.2 mg, 0.009 mmol) was added in a single portion to a stirred solution of the vinyl iodide **17** (23 mg, 0.03 mmol) in DMSO-THF (3:1, 4.8 ml) at room temperature under argon. The mixture was stirred at room temperature for 16 h, then cooled to 15 °C and diluted sequentially with hexane (2 ml) and DL-serine (1M in saturated sodium bicarbonate solution; 6 ml). The mixture was stirred vigorously for 30 min and then the organic layer was separated. The aqueous phase was extracted with diethyl ether (4 × 3 ml) and then the combined organic layers were washed with brine (2 × 20 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica using diethyl ether – pentane (30:70 to 50:50) as eluent to give i) the α-alcohol (4.5 mg, 25%) as a colourless oil, δ_H (360 MHz, $CDCl_3$) 7.30-7.27 (2H, m, *Ar*), 6.91-6.87 (2H, m, *Ar*), 5.28 (1H, br, d, *J* 8.0, C=C*H*CHOH), 5.08-5.04 (1H, br, d, *J* 8.0, C*H*OH), 4.96-4.94 (1H, br. s, O*H*), 4.86 (1H, d, *J* 7.0, OC*H*HO), 4.75-4.70 (2H, m, OCH*H*O and $CH_3C{=}CHCH_2$), 4.54 (1H, d, *J* 11.1, C*H*HOAr), 4.42 (1H, d, *J* 11.1, CH*H*OAr), 4.22 (1H, br. d, *J* 10.8, CC*H*HOCH$_2$), 3.95 (1H, dd, *J* 9.0 and 6.7, C*H*OCH$_2$), 3.81 (3H, s, OCH_3), 3.74 (1H, d, *J* 10.8, CCH*H*OCH$_2$), 3.45 (3H, s, OCH_3), 2.40-1.48 (11H, m, 5 × CH_2 and C*H*), 1.74 (3H, d, *J* 0.7, CH_3C=CH), 1.51 (3H, s, CH_3C=CH), 0.86 (3H, s, CH_3C), 0.85 (3H, obs. d, CH_3CH); δ_C (90 MHz, $CDCl_3$) 159.5 (s), 142.6 (s), 141.4 (s), 133.0 (s), 132.7 (s), 130.3 (d), 129.0 (s), 128.2 (d), 127.7 (d), 113.8 (d), 96.0 (t), 76.5 (d), 72.8 (t), 68.2 (d), 67.4 (t), 55.9 (q), 55.3 (q), 41.8 (s), 36.3 (t), 34.6 (t), 33.6 (t), 33.0 (t), 29.9 (d), 25.8 (t), 21.2 (q), 18.1 (q), 15.7 (q), 15.4 (q) and ii) the β-alcohol (5 mg, 27%) as a colourless oil, δ_H (360 MHz, $CDCl_3$) 7.33-7.31 (2H, m, *Ar*), 6.91-6.89 (2H, m, *Ar*), 5.60 (1H, d, *J* 10.7, C=CHC*H*OH), 5.28 (1H, br. d, *J* 10.7, C=C*H*CHOH), 5.01 (1H, br. s, O*H*), 4.89 (1H, d, *J* 7.0, OC*H*HOCH$_3$), 4.82-4.74 (2H, m, C=C*H*CH$_2$ and C*H*OCH$_3$), 4.73 (1H, d, *J* 7.0, OCH*H*OCH$_3$), 4.47 (2H, br. s, ArCH_2O), 3.82 (3H, s, OCH_3), 3.66 (1H, br. d, *J* 11.2, C*H*HO), 3.50 (1H, d, *J* 11.2, CH*H*O), 3.46 (3H, s, OCH_3), 2.47-2.32 (1H, m, C*H*H), 2.14-1.50 (9H, m, 3 × CH_2, CH*H* and C*H*), 1.60 (3H, d, *J* 1.1, CH_3C=CCHCHOH), 1.44 (3H, s, CH_3C=CH), 0.88 (3H, s, CH_3C), 0.85 (3H, d, *J* 6.8, CH_3CH); δ_C (90 MHz, $CDCl_3$) 159.3 (s), 141.2 (s), 138.4 (s), 135.5 (s), 132.5 (s), 130.3 (s), 129.8 (d), 128.1 (d), 127.5 (d), 113.8 (d), 94.7 (t), 75.6 (d), 72.7 (t), 69.8 (d), 65.6 (t), 56.7 (q), 55.3 (q), 41.1 (s), 38.4 (t), 34.6 (t), 33.4 (t), 31.8 (t), 30.2 (d), 26.9 (t), 21.0 (q), 16.1 (q), 15.8 (q), 15.1 (q); m/z (ES^+) 507.3067 (M^++Na), $C_{30}H_{44}O_5Na$ requires 507.3086.

(16) We thank Dr C. Wilson for the X-ray structure determination, which will be published separately in a full paper.

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