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Tetrahedron Letters 44 (2003) 2713–2716

TETRAHEDRON LETTERS

Approaches to the total synthesis of phomactins

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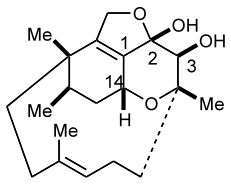
Received 14 January 2003; accepted 4 February 2003

Abstract—The macrocyclic triene **34**, an advanced intermediate for synthesis of phomactins, has been synthesized using the 2,3-Wittig rearrangement of the propargylic ether **21** as a key step.

The phomactins, e.g. A **1**, D **2**, E **3**, and Sch. 49028 **4**, are diterpenes with novel structures and biological activity as platelet activating factor antagonists.[1] Several groups have reported synthetic studies[2] directed towards the phomactins, including total syntheses of phomactin D **2**[3] and A **1**.[4]



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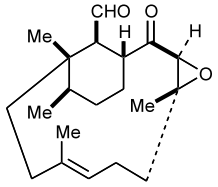

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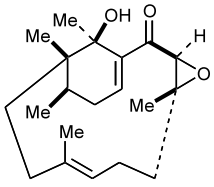

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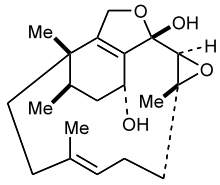
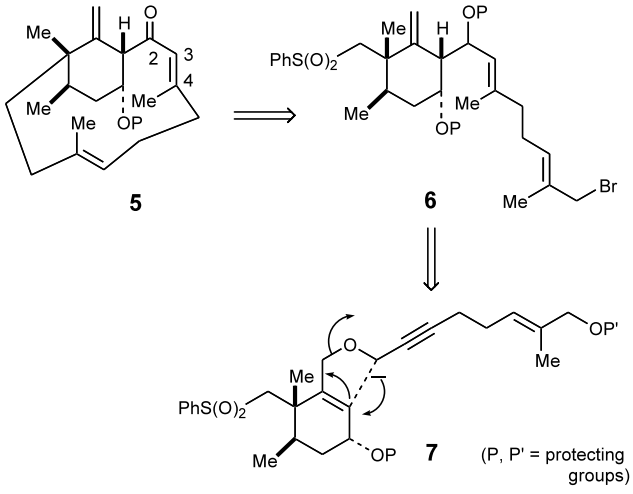


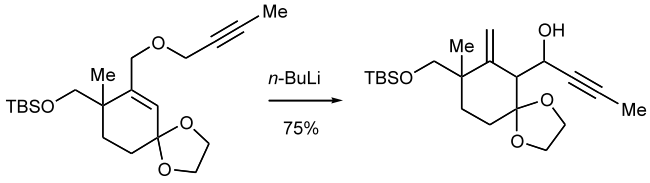
4

An approach to the phomactins can be envisaged in which the trienyl ketone **5** is an advanced intermediate able to provide access to several members of the phomactin family. For example, stereoselective reduction of the ketone followed by hydroxyl directed epoxidation of the 3,4- and exocyclic double-bonds, reoxidation to the bis-epoxyketone and isomerisation of the exocyclic β,γ-epoxide, should lead to Sch. 49028 **4** and hence to phomactin A **1** after deprotection.[5] Similar schemes could be devised to access phomactins D and E from ketone **5**.



5 **6** **7** (P, P' = protecting groups)

By analogy with the synthesis of phomactin D,[3] ketone **5** should be accessible by cyclisation of sulfone **6** which could be synthesized by a 2,3-Wittig rearrangement of a suitable (cyclohexenyl)methyl ether.[6] Preliminary studies have shown that whereas rearrangement of (cyclohexenyl)methyl dimethylallyl ethers takes place with the undesired regioselectivity, rearrangement of analogous propargyl ethers gives the required regioisomers, e.g. **8** gives **9** albeit as a mixture of diastereoisomers.[7,8] On this basis, the propagylic ether **7** was identified as a suitable substrate for the Wittig rearrangement with the conversion of the alkyne into the trisubstituted double-bond to be carried out either before or after macrocyclisation. We here report a synthesis of the bicyclic trienyl alcohol **34**, a congener of the ketone **5** based on this strategy.



8 **9**

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0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00341-1

The synthesis of the Wittig rearrangement precursor **21** is outlined in Scheme 1. Dissolving metal reduction[9]–methylation of *o*-toluic acid **10** followed by esterification and allylic oxidation[10] gave the cyclohexadienone **11**. Conjugate addition of the lower order lithium dimethylcuprate to **11** was regioselective for the less substituted double-bond, and stereoselective for addition *cis* to the methyl substituent, giving the cyclohexenone **12** as the major product,[11] stereoselectivity ca. 85:15, although the stereoisomers were not usually separated at this stage. Free-radical bromination then gave a mixture of the corresponding bromomethyl compounds from which the required major isomer **13** was separated by chromatography. Luche reduction of the enone was highly stereoselective giving alcohol **14** and protection of the alcohol gave the SEM-ether **15**.[12]

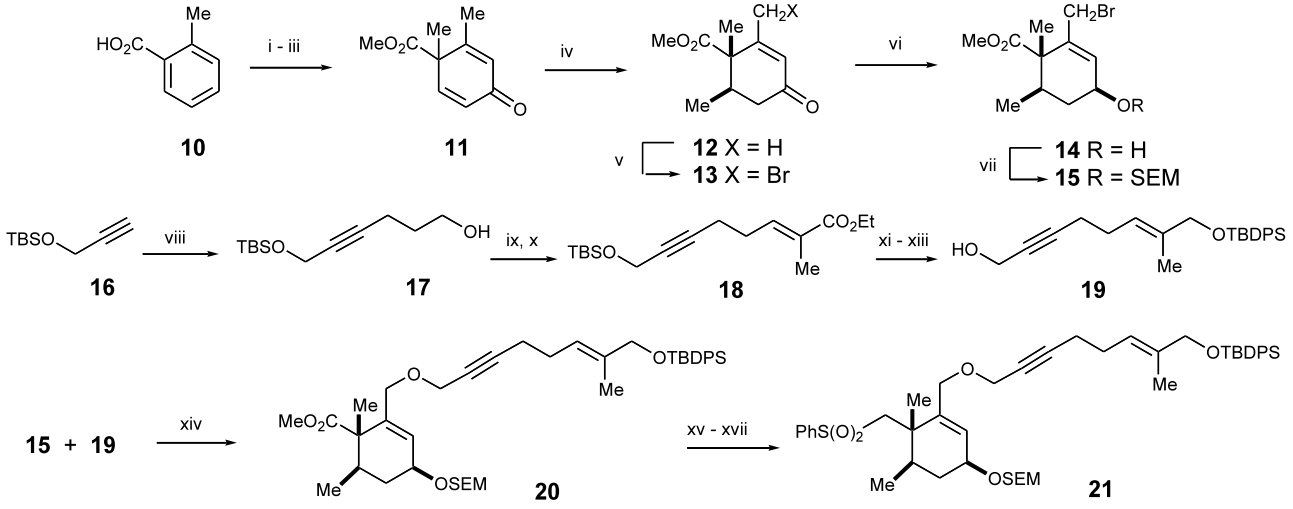
The configuration of the hydroxyl group in the alcohol **14** is the opposite of that required at C-14 for incorporation into phomactin A **1** and Sch. 49028 **4**. However, the configuration at this centre was not changed at this stage since it was thought that macrocyclisation of intermediates with the unnatural configuration at C-14 (phomactin numbering) would be less susceptible to steric hindrance.

The acetylenic component **19** was prepared from the protected propargylic alcohol **16** by reaction of the corresponding lithium acetylide with oxetane[13] to give the alcohol **17**. A Wittig reaction of the corresponding aldehyde then gave the (*E*)-α,β-unsaturated ester **18** and a reduction, protection and selective deprotection sequence led to the required alcohol **19**. Alkylation[14] of this alcohol using the cyclohexenylmethyl bromide **15** gave the ether **20** which was taken through to the required sulfone **21** by reduction and substitution of the mesylate of the alcohol so obtained with sodium thiophenoxide to give a sulfide. Oxidation of the sulfide to the sulfone **21** was complicated by the presence of the trisubstituted double bonds, but was best achieved using ammonium molybdate and hydrogen peroxide in methanol.[15] Under these conditions an acceptable, 65%, yield of the sulfone **21** was obtained together with some of the intermediate sulfoxide which could be separated and oxidised to give more sulfone.

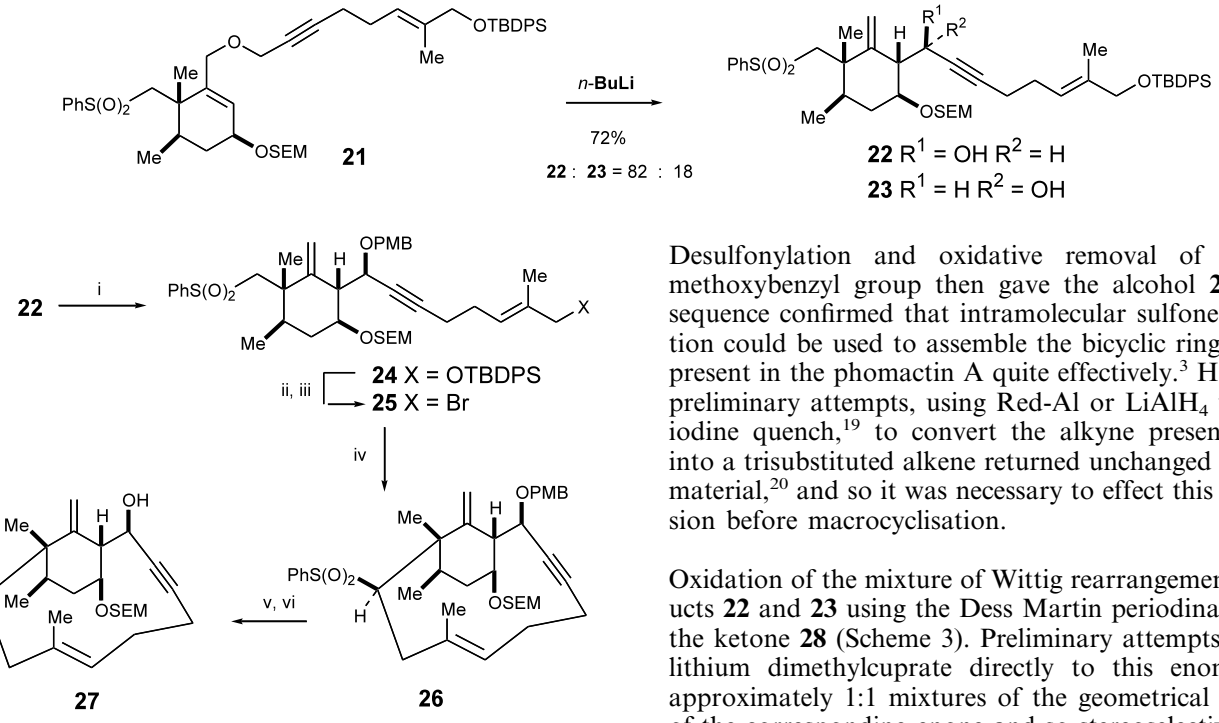
The 2,3-Wittig rearrangement of the sulfone **21** was carried out using 2.5 equivalents of *n*-butyllithium at −78°C and gave an 82:18 mixture of the rearrangement products **22** and **23**. The configurations of these at C-1 were established by NMR but the configurations of the hydroxyl bearing carbons were not confirmed until later in the synthesis.[16]

At this point it was necessary to decide whether to form the macrocyclic ring first and then convert the alkyne into the required trisubstituted alkene en route to the target ketone **5**, or to introduce the alkene before macrocyclisation. In order to gain experience of the macrocyclisation procedure, it was decided to study the former option first.[17]

The major Wittig rearrangement product **22** was protected as its *p*-methoxybenzyl ether **24** which was converted into the allylic bromide **25** by selective removal of the *tert*-butyldiphenylsilyl ether, mesylation and displacement of the allylic mesylate using lithium bromide (Scheme 2). Cyclisation was achieved by syringe pump addition (over 1 h) of sodium hexamethyldisilazide to a solution of the sulfone-bromide in THF at 0°C and,



Scheme 1. *Reagents and conditions*: (i) Li, liq. NH_3, THF, −78°C then MeI (91%); (ii) AcCl, MeOH, rt (88%); (iii) PDC, Celite, TBHP, C_6H_6, 0°C (90%); (iv), $LiCuMe_2$, toluene, 0°C (88%; 80:20); (v) NBS, AIBN, CCl_4, heat under reflux (72%); (vi) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78°C (91%); (vii) SEM-Cl, *i*-Pr_2NEt, DCM, 0°C–rt (80%); (viii) *n*-BuLi, oxetane, $BF_3{\cdot}Et_2O$, −78°C (85%); (ix) DMSO, $(COCl)_2$, Et_3N, DCM, −78°C–rt; (x) $Ph_3PCMe{\cdot}CO_2Et$, −78°C–rt (91% from **17**); (xi) $LiBHEt_3$, THF, −78°C (84%); (xii) TBDPS-Cl, imid., DCM, 0°C (67%); (xiii) 1:1 MeOH:CCl_4, 50°C, sonicate (86%); (xiv) NaH, 15-crown-5, TBAI, THF, rt (65%); (xv) $LiBHEt_3$, THF, 0°C (88%); (xvi) (a) MsCl, Et_3N, DCM, 0°C, (b) NaSPh, DMF, heat under reflux (85%); (xvii) ammonium molybdate, H_2O_2, EtOH, −20°C–rt (65%).



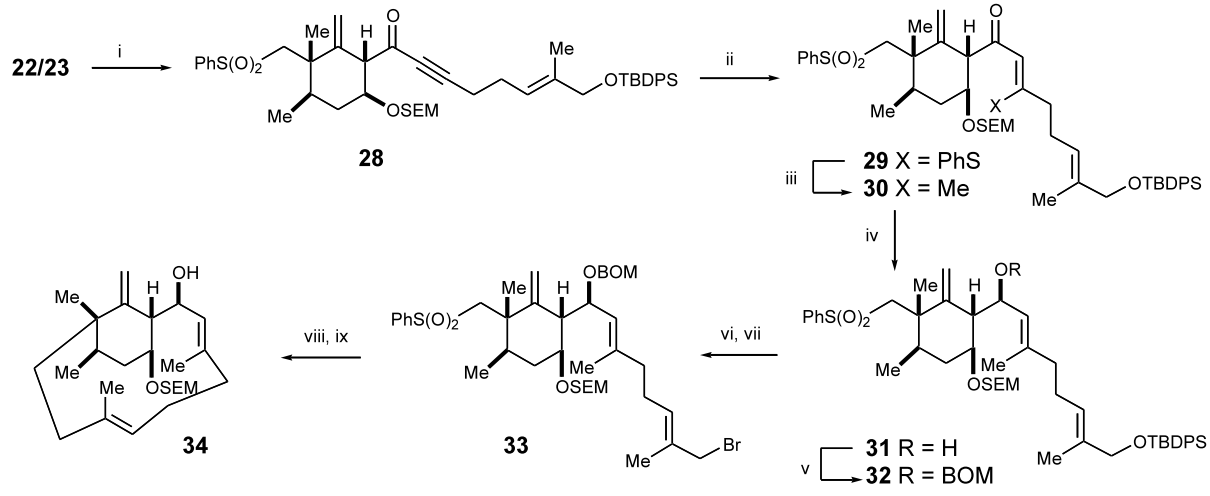
Scheme 2. *Reagents and conditions*: (i) NaH, PMB-Cl, TBAI, DMF, THF, 0°C–rt (58%); (ii) TBAF, THF, rt (87%); (iii) MsCl, Et_3N, DCM, rt, 30 min then LiBr, acetone, 0°C, 30 min (92%); (iv) NaHMDS, THF, 0°C, 1.5 h (68%); (v) 5% Na/Hg, Na_2HPO_4, MeOH, THF, 0°C (93%); (vi) DDQ, pH 7, DCM, H_2O (72%).

after stirring for an extra 30 min, gave a 68% yield of macrocyclic product which was isolated essentially as the single diastereoisomer **26**.

The indicated stereochemistry was assigned to this macrocyclic product on the basis of NMR experiments.[18] Of interest is the fact that high dilution conditions were not necessary for this cyclisation with 90 mg (0.119 mmol) of **25** being cyclised in 1.5 cm^3 THF. Desulfonylation and oxidative removal of the *p*-methoxybenzyl group then gave the alcohol **27**. This sequence confirmed that intramolecular sulfone alkylation could be used to assemble the bicyclic ring system present in the phomactin A quite effectively.[3] However, preliminary attempts, using Red-Al or $LiAlH_4$ with an iodine quench,[19] to convert the alkyne present in **27** into a trisubstituted alkene returned unchanged starting material,[20] and so it was necessary to effect this conversion before macrocyclisation.

Oxidation of the mixture of Wittig rearrangement products **22** and **23** using the Dess Martin periodinane gave the ketone **28** (Scheme 3). Preliminary attempts to add lithium dimethylcuprate directly to this enone gave approximately 1:1 mixtures of the geometrical isomers of the corresponding enone and so stereoselective addition of benzenethiol was investigated. Using a methanolic solution of benzenethiol and triethylamine,[21] a separable 72:28 mixture of the (*Z*)- and (*E*)-vinyl sulfides was obtained from which the required (*Z*)-isomer **29** could be isolated in a 69% yield. Treatment of this sulfide with lithium dimethyl cuprate then gave the required (*E*)-alkene **30**, with retention of configuration, in excellent yield.[22]

Considerable difficulty was experienced during attempts to reduce the ketone **30** to the alcohol **31**; the recovered starting material was obtained using Luche's conditions and over-reduction with $LiAlH_4$. In the end, the reduction was achieved using $NaBH_4$ in ethanol, but only in a 57% yield. Nevertheless this alcohol was protected as its benzyloxymethyl (BOM) ether **32**, and selective



Scheme 3. *Reagents and conditions*: (i) DMP, DCM, rt (89%); (ii) PhSH, Et_3N, THF, MeOH, –20°C (69% together with 26% of the 3,4-(*E*)-isomer); (iii) $LiCuMe_2$, Et_2O, –78°C (97%); (iv) $NaBH_4$, EtOH, rt (57%); (v) BOM-Cl, *i*-Pr_2NEt, TBAI, THF, rt (85%); (vi) TBAF, THF, rt (79%); (vii) MsCl, Et_3N, DCM then LiBr, acetone (69%); (viii) NaHMDS, THF, 0°C; (ix) Na, liq. NH_3, THF, EtOH, –60°C (45% from **33**).

deprotection of the primary alcohol and conversion into the allylic bromide **33** was carried out as before. Macrocyclisation was achieved using syringe pump addition of sodium hexamethyldisilazide and simultaneous removal of the phenyl sulfone and BOM groups gave the required bicyclic trienyl alcohol **34** in a 45% yield over both the cyclisation and reduction steps.

The alcohol **34** corresponds to the key intermediate ketone **5** albeit with the opposite configuration at C-14. Present work is concerned with the development of the final stages of a synthesis of phomactins from this alcohol.

Acknowledgements

We thank the EPSRC for support (to A.S.B., G.M. and P.D.P.S.), GlaxoSmithKline and Merck Sharp and Dohme for CASE awards (to P.D.P.S. and G.M., respectively), Dr. D. Morgan (GSK) and Dr. L. Street (MSD) for helpful discussions, and the EPSRC mass spectrometry service at Swansea for mass spectra.

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11. The stereochemistry of the major enone **12** was confirmed by X-ray diffraction. Details will be published in a full paper.
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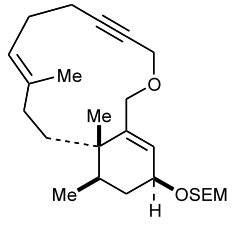
16. The configuration at C-1 (phomactin numbering) in both **22** and **23** also follows from their successful conversion into the bicyclic intermediates **27** and **34**.
17. An alternative approach was also investigated which involved cyclisation of ether **21** to give the macrocyclic ether **i**. However, attempts to effect the required 2,3-Wittig rearrangement of **i** were unsuccessful, perhaps because of ring strain in the product. Details will be published in a full paper.



i

18. Coupling constants and NOE observations established the configurations indicated at C-2 and C-10 (phomactin numbering) in **26**.
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