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The first synthesis of the epoxide-containing macrolactone nucleus of oximidine I

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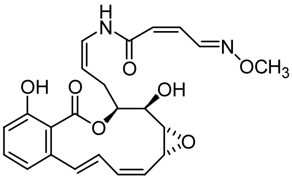
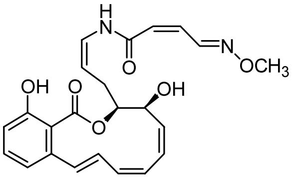
Abstract—A synthesis of the epoxydiene-containing macrolide nucleus of oximidine I is reported, starting from commercially available 3-butyn-1-ol. The key macrocyclisation step is achieved using Horner–Wadsworth–Emmons methodology in the presence of an epoxide.

Oximidines I and II (**1** and **2**) were recently isolated[1] from *Pseudomonas* sp. Q52002 and are part of an expanding family of cytotoxic natural products based on a salicylate-macrolactone core having a pendant unsaturated enamide side-chain. Other members of this family include salicylihalamide A,[2] apicularen A[3] and lobatamide C[4] which have all succumbed to total synthesis. This class of compound exhibits significant and selective cytotoxicity towards *ras* and *src* oncogene-transformed cells, with mammalian vacuolar-type (H^+)-ATPases being the cellular targets.[5]



Oximidine I (**1**)



Oximidine II (**2**)

There has been considerable work towards the synthesis of the complex conjugated enamide *O*-methyl oxime side-chain present in the oximidines and lobatamides.[6] In addition, there have been two published syntheses of model systems related to the macrocycles of oximidine I and II.[7,8] Very recently, Porco and Wang have reported an elegant total synthesis of oximidine II which makes use of alkene metathesis in the key ring-closing step.[9] Nevertheless, the epoxydiene functionality of oximidine I has remained elusive. In connection with our on-going research into synthetic routes to this class of natural product, we were attracted to the possibility of macrocyclisation in the presence of an epoxide, as there are potential pitfalls associated with subsequent introduction of this moiety. Furthermore, methods are known for the conversion of epoxides into alkenes,[10] and so the triene system of oximidine II might also be accessible by this route. While epoxides are generally thought of as extremely reactive functional groups, there is some evidence that they can survive a variety of reaction conditions.[11] We decided to tackle the synthesis of the target model macrocycle **3** (Scheme 1) from two angles: namely, intermolecular Horner–Wadsworth–Emmons (HWE) reaction followed by macrolactonisation (route a); and esterification with subsequent intramolecular HWE reaction (route b).

The known *cis*-epoxy aldehyde **4**,[12] which was common to both our proposed routes, was prepared from 3-butyn-1-ol (**5**) via a modification of the original sequence (Scheme 2). Stabilised Wittig reaction of this intermediate with (ethoxycarbonylmethylene)triphenylphosphorane was carried out in methanol to enhance the *Z*-selectivity[13] and this afforded the conjugated ethyl ester **6** (alkene coupling $J = 11.8$ Hz) as a 5:1 mixture with its *E*-isomer (alkene coupling $J = 15.8$ Hz).[14] The isomers were separable and DIBAL-H reduction of *Z*-**6** to the aldehyde **7** occurred in 74% yield.

The aryl methyl phosphonate **10** (Scheme 3) was prepared from commercially available methyl 2-methylbenzoate (**8**) via the intermediate bromide **9**. The (trimethylsilyl)ethyl ester **12** (vide infra) was accessible from **10** by saponification to acid **11** and subsequent carbodiimide-promoted esterification.

Keywords: oximidine; Horner–Wadsworth–Emmons; epoxide.

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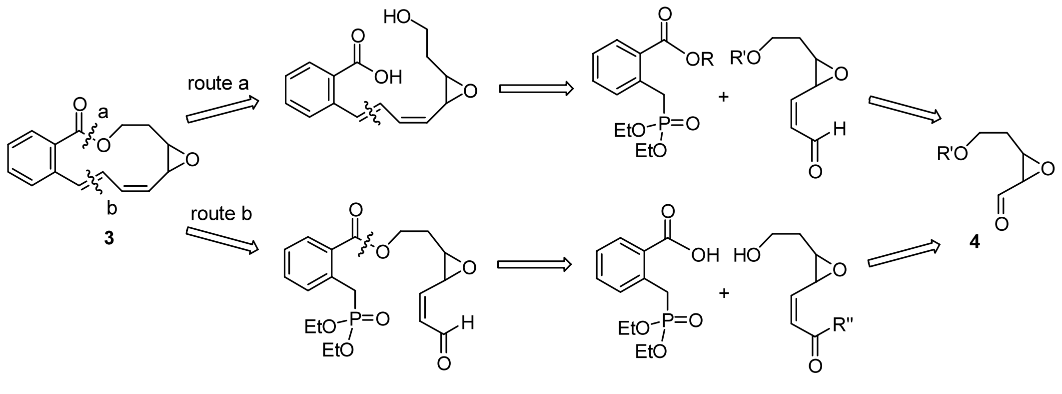
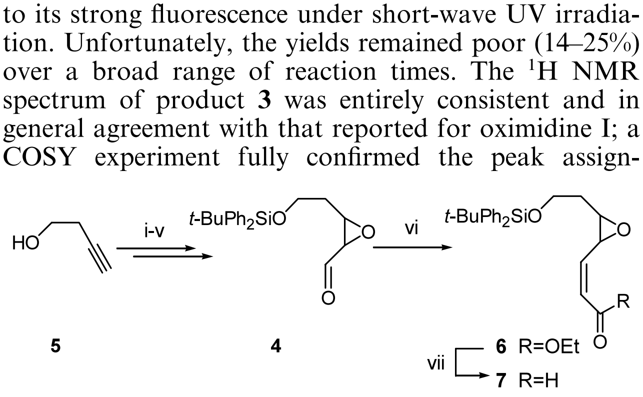


Scheme 1.

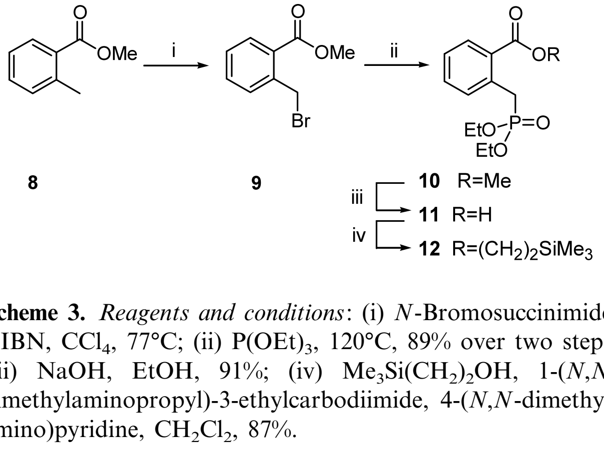
We were now in a position to evaluate the HWE-macrolactonisation approach (Scheme 4). Thus, base-treatment of compounds **7** and **10** afforded epoxydiene **13** in 36% yield. Desilylation proceeded smoothly but subsequent saponification did not give the expected hydroxy acid **14**. Instead, phthalide **15** was the only identifiable component of the reaction mixture. Compound **15** presumably forms by 5-*exo*-*trig* cyclisation of the acid carboxylate in the desired product **14** on to the epoxydiene system with concomitant opening of the epoxide. In an effort to avoid the problematic saponification step, the (trimethylsilyl)ethyl ester **12** was subjected to HWE reaction with aldehyde **7** to provide the diene **16** in excellent yield (77%) (Scheme 4). Unfortunately, when this was treated with tetra-*n*-butylammonium fluoride for double-desilylation, the phthalide **15** again formed.

These problems encouraged investigation of the alternative route: esterification followed by final intramolecular HWE reaction (Scheme 5). Thus, *Z*-selective Wittig reaction of the aforementioned aldehyde **4** to afford *Z*-methyl ester **17** (alkene coupling $J=11.8$ Hz), followed by reduction gave the allylic alcohol **18**. The efficacy of this reduction was highly dependant on the quality of the DIBAL-H reagent. More reproducible results could be obtained by performing the reduction in two stages with aqueous workup after each stage. Protection as the acetate **19** and desilylation provided alcohol **20** in high yield. After Yamaguchi-type activation of aryl acid **11**, the alcohol **20** was added and ester **21** was obtained in 70% yield. Deacetylation proved challenging, giving the dihydrofuran **22** under standard conditions.[15] Eventually it was found that treatment of the acetate **21** with Cs_2CO_3 and triethylamine in methanol at 0°C for 30 min gave solely the desired allylic alcohol **23** (88% yield). Pyridinium dichromate oxidation of alcohol **23** was accompanied by isomerisation of the *Z*-double bond, while attempted in situ manganese dioxide oxidation/HWE reaction[16] gave dihydrofuran **24**, resulting from cyclisation by the alcohol onto the epoxide functionality and ester cleavage. Nevertheless, Swern oxidation cleanly gave aldehyde **25** in an excellent 86% yield.

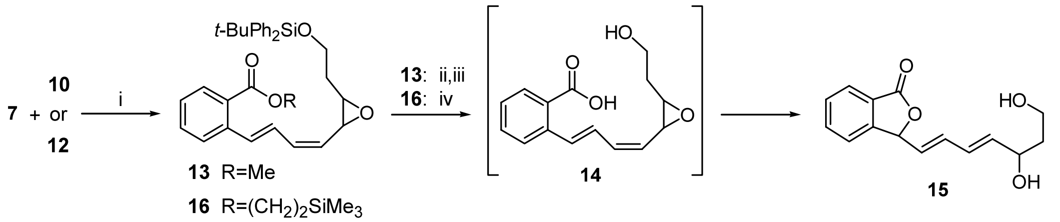
A number of bases were tested for the key intramolecular HWE: only KO^{t}Bu and KHMDS afforded the desired product **3**. After much optimisation of conditions, it was found that KO^{t}Bu in the presence of 18-crown-6 at 70°C in toluene furnished the macrocycle **3** with the highest reproducibility. Formation of the highly conjugated product **3** was obvious by TLC due to its strong fluorescence under short-wave UV irradiation. Unfortunately, the yields remained poor (14–25%) over a broad range of reaction times. The ^{1}H NMR spectrum of product **3** was entirely consistent and in general agreement with that reported for oximidine I; a COSY experiment fully confirmed the peak assign-



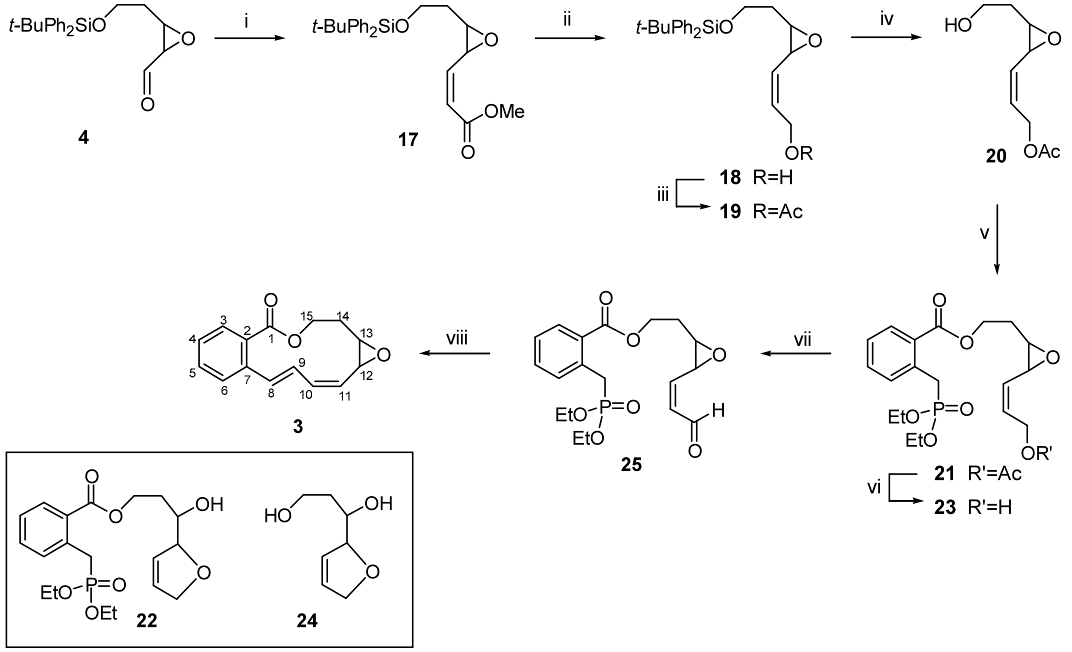
Scheme 2. *Reagents and conditions*: (i) ^{t}BuPh$_2$SiCl, imidazole, DMF, 92%; (ii) (a) ^{n}BuLi, Et_2O, −78°C, (b) $(CH_2O)_n$, −78 to 20°C, 74%; (iii) H_2, Lindlar's catalyst, quinoline, MeOH; (iv) ^{t}BuOOH, VO(acac)$_2$, 4 Å molecular sieves, toluene, 74% over two steps; (v) pyridinium dichromate, 4 Å molecular sieves, CH_2Cl_2, 76%; (vi) $Ph_3P{=}CHCO_2Et$, NEt_3, MeOH, −10 to 0°C, 85% (5:1 *Z*:*E* mixture); (vii) DIBAL-H, CH_2Cl_2, −75°C, 74%.



Scheme 3. *Reagents and conditions*: (i) *N*-Bromosuccinimide, AIBN, CCl_4, 77°C; (ii) $P(OEt)_3$, 120°C, 89% over two steps; (iii) NaOH, EtOH, 91%; (iv) $Me_3Si(CH_2)_2OH$, 1-(*N*,*N*-dimethylaminopropyl)-3-ethylcarbodiimide, 4-(*N*,*N*-dimethylamino)pyridine, CH_2Cl_2, 87%.



Scheme 4. *Reagents and conditions*: (i) KO^{t}Bu, THF, −10°C, 36% (**13**), 77% (**16**); (ii) ^{n}Bu$_4$NF, THF, −10 to 20°C, 75%; (iii) LiOH, THF, MeOH, H$_2$O; (iv) ^{n}Bu$_4$NF, dimethylsulfoxide, 39%.



Scheme 5. *Reagents and conditions*: (i) Ph$_3$P=CHCO$_2$Me, NEt$_3$, MeOH, −15°C, 93% (5:1 *Z*:*E* mixture); (ii) DIBAL-H (2×1.3 equiv.), CH$_2$Cl$_2$, −78°C, 74%; (iii) Ac$_2$O, pyridine, CH$_2$Cl$_2$, 84%; (iv) ^{n}Bu$_4$NF, THF, −15 to 10°C, 92%; (v) **11**, 2,4,6-trichlorobenzoyl chloride, NEt$_3$, THF then **20**, 4-(*N*,*N*-dimethylamino)pyridine, toluene, 70%; (vi) Cs$_2$CO$_3$, NEt$_3$, MeOH, 0°C, 88%; (vii) Me$_2$SO, (ClCO)$_2$, CH$_2$Cl$_2$, −78°C then NEt$_3$, 86%; (viii) KO^{t}Bu, 18-crown-6, toluene, 70°C, 14–25%.

ments.[17] Significantly, the alkene proton corresponding to H-11 appeared as a doublet (δ 5.61, $^3J_{10,11}=10.1$ Hz), while the epoxide peak H-12 was a broad singlet (δ 3.71, $^3J_{12,13}$ not resolved) suggesting a near-perpendicular relationship between these protons, as seen in the natural product.[1] Full ^{13}C and 2D NMR data were obtained which further confirmed the assigned structure. The mass spectra were also in agreement with the structure of the macrocycle. Finally, the UV spectrum of the product showed a maximum at 276 nm (ε 24,205) which compares with the natural product value of 272 nm (ε 30,500).[1]

In conclusion, the epoxy-diene macrolide **3** has been prepared from the known aldehyde **4** in eight steps (4–8% overall yield) using Horner–Wadsworth–Emmons methodology for the key cyclisation. This synthesis of a simplified version of the anti-tumour natural product oximidine I has allowed the development of methodology, particularly with respect to maintenance of the epoxide moiety, which may aid efforts towards the natural product itself. Our application of this approach towards the synthesis of oximidine I is continuing.

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17. Compound **3**: clear, colourless oil, $R_f = 0.28$ (1:7, EtOAc/petrol). Found (CI): 243.1025. $C_{15}H_{15}O_3$ requires [MH$^+$]: 243.1021 (1.6 ppm error). m/z (CI) 260 (M+NH$_4^+$, 38%), 243 (MH$^+$, 100), 225 (17). ν_{max}/cm^{-1} (thin film) 3056, 2921, 2852, 1733, 1267, 739. UV/vis (MeOH) λ_{max} 276 nm ($\varepsilon = 24,205$). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (d, J 7.6 Hz, 1H, H3), 7.43 (dd, J 7.6, 7.3 Hz, 1H, H5), 7.32 (dd, J 7.6, 7.3 Hz, 1H, H4), 7.28 (partially obscured d, 1H, H6), 6.67 (d, J 15.9 Hz, 1H, H8), 6.54 (dd, J 15.9, 11.0 Hz, 1H, H9), 6.37 (dd, J 11.0, 10.1 Hz, 1H, H10), 5.61 (d, J 10.1 Hz, 1H, H11), 5.07 (t, J 11.9 Hz, 1H, H15), 4.13 (dt, J 11.9, 3.0 Hz, 1H, H15), 3.71 (broad s, 1H, H12), 3.34 (dd, J 9.8, 3.1 Hz, 1H, H13), 2.13 (dd, J 15.9, 3.0 Hz, 1H, H14), 1.70 (dddd, J 15.9, 11.9, 9.8, 3.0 Hz, 1H, H14). ^{13}C NMR (125 MHz, CDCl$_3$) δ 170.6 (C), 137.3 (C), 132.4 (CH), 131.6 (C), 130.9 (CH), 130.5 (CH), 130.1 (2×CH), 129.7 (CH), 127.5 (CH), 125.7 (CH), 61.9 (CH$_2$), 58.3 (CH), 55.8 (CH), 29.1 (CH$_2$).