Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 5751–5758
Tetrahedron

Synthesis of pyrrolo[3,2-*b*]benzofurans and pyrrolo[3,2-*b*]naphthofurans via addition of a silyloxypyrrole to activated quinones

Margaret A. Brimble,* Caryn Burgess, Rosliana Halim, Maria Petersson and Jayanta Ray

Department of Chemistry, University of Auckland, 23 Symonds St., Auckland 1000, New Zealand

Received 15 March 2004; revised 13 April 2004; accepted 6 May 2004

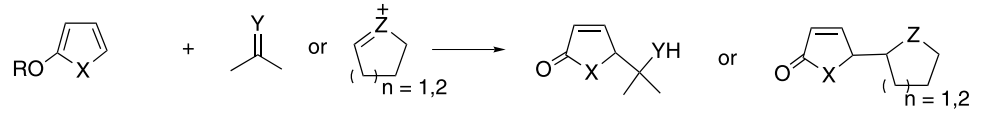
Abstract—The uncatalyzed reaction of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** with 1,4-quinones bearing an electron withdrawing group at C-2 has been studied. Use of 1,4-quinones **4**, **5** bearing an ester group at C-2 provided an efficient synthesis of the respective pyrrolidinobenzofuran adduct **9** or pyrrolidinonaphthofuran adduct **10** whereas use of 1,4-quinones **6**, **7** and **8** bearing an acetyl group at C-2 afforded silyloxypyrroles **11**, **12** and **13** resulting from direct electrophilic substitution of the silyloxypyrrole by the electrophilic quinone. Addition of $Eu(fod)_3$ to the reaction of 2-acetyl-1,4-naphthoquinone **7** and 3-acetyl-5-methoxy-1,4-naphthoquinone **8** with *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole **3** provided a method for obtaining the pyrrolidinonaphthofuran adducts **14** and **15** together with silyloxypyrroles **12** and **13**. Oxidative rearrangement of pyrrolidinonaphthofuran adduct **15** to pyrrolidino pyranonaphthoquinone **16** using ceric ammonium nitrate in acetonitrile provided a novel approach for the synthesis of an aza-analogue of the pyranonaphthoquinone antibiotic kalafungin.

1. Introduction

The silyl enolate d^4 synthons 2-trimethylsilyloxyfuran (TMSOF) **1**, 2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** and *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrrole (TBSOP) **3** readily undergo vinylogous aldol-like reactions[1] with aldehydes, vinylogous imino–aldol reactions[2] (Mannich type addition) with imines and vinylogous addition to heteroatom-stablized carbenium ions (Scheme 1).[3] The resultant aldol-like products provide ready access to many bioactive molecules including the Annonaceous acetogenins,[4,5] carbasugars,[6] densely hydroxylated indolizidine alkaloids,[7] hydroxylated prolines,[8] aminosugars[9] and peptidyl *C*-glycosides.[10]

As an extension to this work we reported[11] the reaction of TMSOF **1** with 1,4-benzoquinones and 1,4-naphthoquinones bearing electron withdrawing substituents at C-2, proceeding via conjugate addition of TMSOF **1** to the 1,4-quinone before intramolecular cyclization to the corresponding furobenzofuran or furonaphthofuran. This atom efficient furofuran annulation formed our key step[12] in the synthesis of several pyranonaphthoquinone antibiotics[13] (e.g., kalafungin) by virtue of the fact that the furonaphthofuran adducts underwent facile oxidative cyclization to a pyranonaphthoquinone skeleton using ceric ammonium nitrate (CAN) (Scheme 2).

Prompted by the idea of preparing aza analogues of the pyranonaphthoquinone antibiotics via rearrangment of the analogous pyrrolidinofuran adducts we undertook a study of the addition of TBSOP **3** to several 1,4-quinones **4**-**8** bearing an electron withdrawing groups at C-2. Our preliminary communication[14] reported that the products obtained from

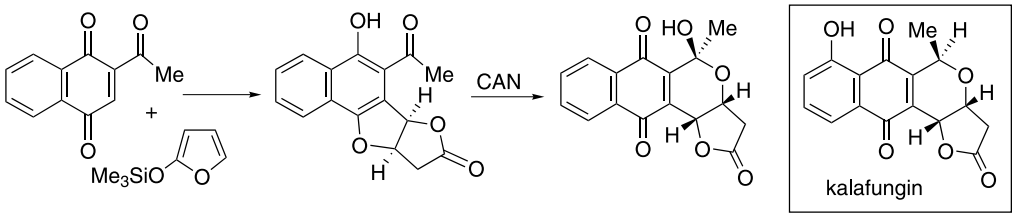


1: X = O; R = $SiMe_3$ Y = O, NH; Z = O, N
2: X = S; R= Si^tBuMe_2
3: X = $NCO_2{}^tBu$; R= Si^tBuMe_2

Scheme 1.

Keywords: Quinones; Pyrrole; Michael addition.
* Corresponding author. Tel.: +64-9-3737599; fax: +64-9-3737422; e-mail address: m.brimble@auckland.ac.nz

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.008



Scheme 2.

these reactions depended on the nature of the substituent at C-2 in the 1,4-quinone. Use of 2-acetyl-1,4-quinones afforded silyloxypyrrole adducts whereas 2-carbomethoxy-1,4-quinones afforded the desired pyrrolidinofuran adducts. We herein report the full details of this study together with a method for obtaining the pyrrolidinonaphthofuran adducts as well as the silyloxypyrrole intermediates in the addition of TBSOP **3** to 2-acetyl-1,4-naphthoquinones **7**,**8**. The pyrrolidinonaphthofuran products had hitherto eluded us. The preparation of pyrrolidinobenzofurans and pyrrolidinonaphthofurans is of interest due to their presence in BODIPY dyes[15] and the alkaloid phalarine.[16]

2. Results and discussion

Despite the fact that TBSOP **3** has been successfully used as a nucleophile in the addition to carbonyl and carbonyl-related compounds[1–3] its use as a nucleophile in Michael additions has been limited to using α-methylene lactones[17] as Michael acceptors. At the outset of this work a study of the addition of TBSOP **3** to quinones had not been reported however Garcia Ruano et al.[18] have since described the diastereoselective addition of TBSOP **3** to 2-(arylsulfinyl)-1,4-benzoquinones proceeding via the intermediacy of an α,β-unsaturated butyrolactam intermediate rather than a silyloxypyrrole intermediate. Earlier work by Eugster et al.[19] describes the addition of pyrroles to acetyl-1,4-quinones.

The synthesis of TBSOP **3** via silylation of 1,5-dihydropyrrol-2-one was carried out according to the previously reported procedure.[20] Quinones **4**,[21] **5**[22] and **6**[23] were prepared by mild oxidation of the corrresponding hydroquinones and quinones **7**[24] and **8**[25] were prepared by oxidation of 2-acetyl-1,4-dimethoxynaphthalene[26] and 3-acetyl-1,5-dimethoxy-4-naphthol,[25] respectively.

Uncatalyzed addition of TBSOP **3** (2.0 equiv.) to 2-methoxycarbonyl-1,4-benzoquinone **4** and 2-methoxycarbonyl-1,4-naphthoquinone **5** in acetonitrile at room temperature afforded pyrrolidinobenzofuran adduct **9** and pyrrolidinonaphthofuran adduct **10** in 36 and 54% isolated yield, respectively (Table 1). The adducts **9** and **10** decomposed substantially upon purification by flash chromatography and purification was also difficult due to the presence of significant quantities of *N*-Boc-pyrrol-2(5*H*)-one formed by thermal decomposition of TBSOP **3**. Adducts **9** and **10** were characterized by the magnitude of the bridgehead coupling constant $J_{3a,8b}$=5.1–5.4 Hz that clearly established the *cis*-fusion of the two five-membered rings.

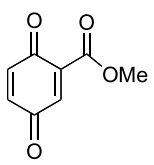
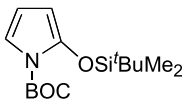
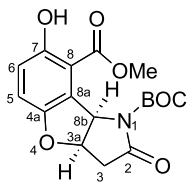
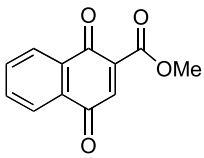
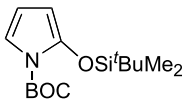
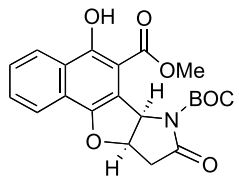
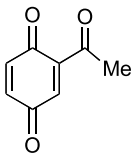
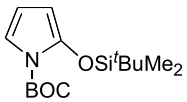
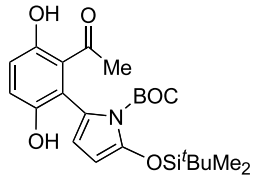
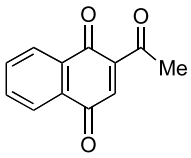
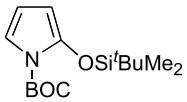
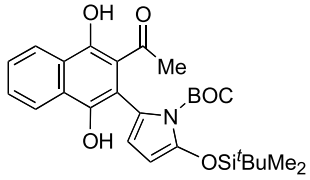
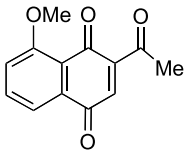
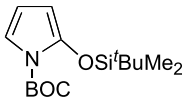
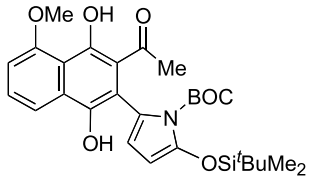
Analogous addition of TBSOP **3** to 2-acetyl-1,4-benzoquinone **6**, 2-acetyl-1,4-naphthoquinone **7** and 2-acetyl-8-methoxy-1,4-naphthoquinone **8** afforded hydroquinone-substituted silyloxypyrroles **11**, **12** and **13** in 56, 64 and 38% isolated yield, respectively. Thus, the use of the more electron deficient 2-acetyl substituted 1,4-quinones afforded products arising from direct electrophilic aromatic substitution of the pyrrole ring. Any evidence for formation of similar silyloxypyrroles in the ^{1}H NMR spectrum of the crude reaction mixtures obtained from addition of TBSOP **3** to the 2-methoxycarbonyl-substituted quinones **4** and **5** was not found.

The related study by Garcia Ruano et al.[18] on the addition of TBSOP **3** to 2-(arylsulfinyl)-1,4-benzoquinones reported the isolation of hydroquinone-substituted α,β-unsaturated butyrolactam intermediates rather than the hydroquinone-substituted silyloxypyrrole intermediates observed in the present work. These observations may be attributed to the reaction of 2-acetyl-1,4-quinones proceeding via a direct electrophilic substitution rather than a Michael addition pathway when using 2-(arylsulfinyl)-1,4-benzoquinones.

Despite the fact that subtle electronic differences in the nature of the quinone used afforded different products, it was hoped that silyloxypyrroles **12** and **13** could be converted to pyrrolidinonaphthofurans **14** and **15** which would then undergo oxidative rearrangement to a pyrrolidino pyranonaphthoquinone. In our earlier communication[14] we reported our inability to effect the smooth conversion of silyloxypyrroles **12** and **13** to the respective pyrrolidinonaphthofurans **14** and **15** using a variety of acidic, basic and fluoride-containing reagents. When the initial addition of TBSOP **3** to 2-acetyl-8-methoxy-1,4-naphthoquinone **8** was carried out in acetonitrile and pyridinium *p*-toluenesulfonate (PPTs) then added directly to the reaction mixture, pyrrolidinonaphthofuran **15** was afforded albeit in 13% yield. Garcio Ruano et al.[18] reported similar difficulties in inducing the cyclization of α,β-unsaturated butyrolactam intermediates to pyrrolidinobenzofurans using acidic conditions and they established that use of Eu(fod)$_3$ as a Lewis acid afforded the optimum yield of the pyrrolidinobenzofuran products rather than the butyrolactam intermediates.

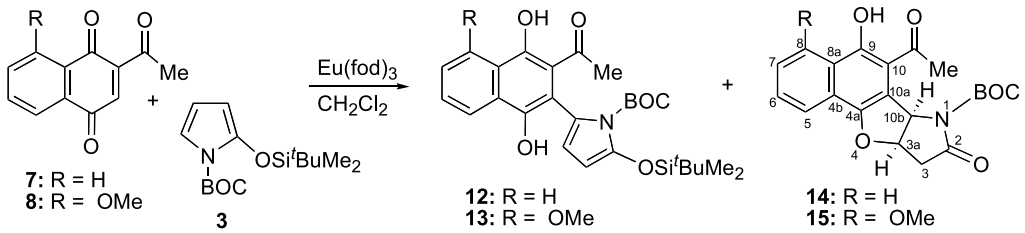
Prompted by the work of Garcia Ruano et al.[18] we subsequently investigated the use of Lewis acids to promote the addition of TBSOP **3** to 2-acetyl-1,4-naphthoquinone **7** hoping to access the pyrrolidinonaphthofuran **14** (Table 2). Use of $ZnBr_2$, $BF_3{\cdot}Et_2O$ and $SnCl_4$ met with little success and analogous to the work by Garcia Ruano et al.[18] the optimum results were obtained using Eu(fod)$_3$ as the Lewis acid.

Table 1. Uncatalyzed addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrole **3** to 2-substituted 1,4-benzoquinones and 1,4-naphthoquinones[a]

Quinone	Reagents	Product and yield %
 **4**		 **9** (36%)
 **5**		 **10** (54%)
 **6**		 **11** (56%)
 **7**		 **12** (64%)
 **8**		 **13** (38%)

[a] All reactions carried out using **3** (2.0 equiv.) in acetonitrile at room temperature for 16 h.

Table 2. $Eu(fod)_3$ catalyzed addition of *N*-(*tert*-butoxycarbonyl)-2-*tert*-butyldimethylsilyloxypyrole **3** to 2-acetyl-1,4-quinones



Quinone (1.0 equiv.)	equiv. of **3**	$Eu(fod)_3$ (equiv.)	Reaction temperature (time)[a]	Products (yield %)
7	2.0	2.0	−78 °C (30 min)	**14** (5%)
7	2.0	1.0	−78 °C (1 h) then rt (16 h)	**12** (46%) **14** (13%)
7	1.0	1.0	−78 °C (1 h) then rt (16 h)	**12** (43%) **14** (33%)
7	1.0	0.5	−78 °C (1 h) then rt (16 h)	**14** (3%)
8	1.0	1.0	−78 °C (1 h) then rt (16 h)	**13** (42%) **15** (38%)

[a] All reactions were carried out in dichloromethane.

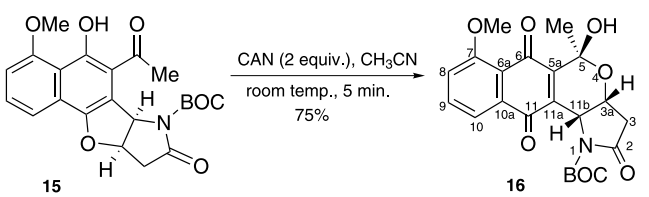
In the first attempt to carry out this reaction, TBSOP **3** (2.0 equiv.) was added to 2-acetyl-1,4-naphthoquinone **7** (1.0 equiv.) and Eu(fod)$_3$ (2 equiv.) in dichloromethane at −78 °C for 30 min. Disappointingly, this procedure afforded the desired adduct **14** in only 5% yield after purification by flash chromatography. In an attempt to improve the yield of the Lewis acid promoted reaction, the reaction was repeated several times varying the ratio of naphthoquinone: pyrrole: Eu(fod)$_3$ as well as extending the reaction time to 16 h.

The optimum conditions (entry 3, Table 2) involved the use of TBSOP **3** (1.0 equiv.), 2-acetyl-1,4-naphthoquinone **7** (1.0 equiv.) and Eu(fod)$_3$ (1.0 equiv.) in dichloromethane at −78 °C for 1 h followed by warming the reaction to room temperature for a further 16 h. This procedure afforded the desired adduct **14** in 33% yield together with silyloxypyrrole **12** in 43% yield. Use of 2.0 equiv. of TBSOP **3** (entry 2, Table 2) afforded less of the desired adduct (13%) and more of the silyloxypyrrole **12** (46%) whilst use of less Eu(fod)$_3$ (0.5 equiv.) (entry 4, Table 2) was ineffective. It was therefore concluded that the use of a stoichiometric quantity of the Lewis acid was necessary for optimum reaction.

Attempts to effect subsequent conversion of the silyloxypyrrole **12** isolated from this reaction to pyrrolidinonaphthofuran **14** using Eu(fod)$_3$ (2.0 equiv.) proceeded in only 5% yield. This result suggests that it is better to use Eu(fod)$_3$ as a Lewis acid in the initial addition of TBSOP **3** to 2-acetyl-1,4-naphthoquinone **7** to achieve optimum formation of pyrrolidinonaphthofuran **14**.

The spectroscopic data obtained for pyrrolidinonaphthofuran **14** supported the formation of the desired product. The high resolution mass spectrum exhibited a molecular ion at *m/z* 383.1371 (M^+) supporting the molecular formula $C_{21}H_{21}NO_6$. The ^{1}H NMR spectrum exhibited a characteristic singlet at δ_H 12.99 that was assigned to the newly introduced hydroxyl group. The characteristic downfield nature of this singlet was attributed to intramolecular hydrogen bonding to the acetyl group. Two single proton doublet of doublets at δ_H 3.02 and 3.13 were assigned to the two geminal H-3 protons consistent with the loss of aromaticity from the starting TBSOP **3**. Further distinctive resonances at δ_H 5.34 (triplet, $J_{3a,10b}$=5.1 Hz) and 5.84 (doublet, $J_{3a,10b}$=5.1 Hz) were assigned to the bridgehead protons H-3a and H-10b respectively. The magnitude of the bridgehead coupling constant, $J_{3a,10b}$=5.1 Hz, was consistent with *cis*-fusion of the two five membered rings.

In a similar fashion addition of TBSOP **3** (1.0 equiv.) to 2-acetyl-8-methoxy-1,4-naphthoquinone **8** (1.0 equiv.) in the presence of Eu(fod)$_3$ (1.0 equiv.) in dichloromethane at



Scheme 3.

−78 °C for 1 h afforded the pyrrolidinonaphthofuran **15** in 38% yield together with silyloxypyrrole **13** in 42% yield. It was then rewarding to find that pyrrolidinonaphthofuran **15** underwent smooth oxidative rearrangement to the desired pyrrolidino pyranonaphthoquinone **16** in good yield (Scheme 3) using ceric ammonium nitrate (CAN). The stereochemistry at the hydroxyl centre in **16** was assigned by analogy to that observed for similar rearrangements of furonaphthofurans to furonaphthopyrans.[12a] The successful formation of pyrrolidino pyranonaphthoquinone **16** provides a novel approch to the basic skeleton required for the synthesis of aza analogues of the pyranonaphthoquinone family of antibiotics such as kalafungin.

In summary a study of the addition of TBSOP **3** to several electron deficient quinones is reported. Uncatalyzed addition of TBSOP **3** to 1,4-quinones **4** and **5** bearing carbomethoxy substituents at C-2, affords pyrrolidinobenzofuran **9** or pyrrolidinonaphthofuran **10**, respectively. In the case of the 2-acetyl-1,4-quinones **6**, **7** and **8** the uncatalyzed reaction affords the silyloxypyrrole intermediates and the use of the Lewis acid Eu(fod)$_3$ is required to obtain significant amounts of the pyrrolidinonaphthofuran adducts. These pyrrolidinonaphthofuran adducts provide novel heterocyclic ring systems that can be further elaborated to provide aza analogues of natural products as demonstrated by the conversion of adduct **15** to an aza analogue **16** of the bioreductive alkylating agent kalafungin.

3. Experimental

3.1. General details

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Spectrum One Fourier-transform infrared spectrophotometer as thin films or Nujol mulls between sodium chloride plates. Proton (^{1}H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 (300 MHz) or a Bruker DRX-400 (400 MHz) spectrometer at ambient temperature. Carbon (^{13}C) NMR spectra were recorded on a Bruker Avance 300 (75 MHz) or a Bruker DRX 400 (100 MHz) spectrometer at ambient temperature with complete proton decoupling. All spectra were recorded using $CDCl_3$ as the solvent with reference to residual $CHCl_3$ (^{1}H at 7.26 ppm and ^{13}C at 77.0 ppm). Low resolution mass spectra were recorded on a VG70-SE double focusing magnetic sector mass spectrometer operating with an ionisation potential of 70 eV. High resolution mass spectra were recorded at nominal resolution of 5000 or 10,000 as appropriate. Major fragments are given as percentages relative to the base peak and assigned where possible. Ionisation methods employed were either electron impact or chemical ionisation with ammonia or methane as reagent gas (CI). Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de-Haen Kieselgel S silica gel (both 230–400 mesh) with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine, alkaline permanganate or vanillin in methanolic sulfuric acid.

Acetonitrile was distilled from calcium hydride immediately before use.

3.1.1. *N*-(*tert*-Butoxycarbony)-2-*tert*-butyldimethylsilyl-oxypyrrole 3. To a solution of *tert*-butyl 2-oxo-1,5-dihydropyrrole-1-carboxylate and *tert*-butyl 2-oxo-1,3-dihydropyrrole-1-carboxylate[20] (2.87 g, 16.5 mmol) in anhydrous dichloromethane (12.0 mL) were added 2,6-lutidine (5.1 g, 47.2 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.64 g, 17.6 mmol) under nitrogen at room temperature. After the reaction mixture was stirred for 30 min, the solvent was removed under reduced pressure to afford a pale yellow oil. The oil was purified by flash chromatography using hexane–ethyl acetate (8:2) as eluent to afford the title compound **3** (3.45 g, 74%) as a yellow oil; δ_H (200 MHz, $CDCl_3$) 0.21 (6H, s, $SiMe_2$), 0.97 (9H, s, $SiMe_2^tBu$), 1.55 (9H, s, ^tBu), 5.21 (1H, dd, J=3.7, 2.0 Hz, H-3), 5.88 (1H, t, J=3.7 Hz, H-4), 6.67 (1H, dd, J=3.7, 2.0 Hz, H-5). The ^1H NMR data was in agreement with that reported in the literature.[27]

3.1.2. 2-Carbomethoxy-1,4-benzoquinone 4. A mixture of methyl 2,5-dihydroxybenzoate[28] (1.0 g, 6.0 mmol) and anhydrous sodium sulfate (1.5 g) in dry toluene (50.0 mL) was stirred with manganese dioxide (5.2 g, 60.0 mmol) for 2 h. The suspension was filtered through sodium sulfate and Celite and the filter cake was washed with toluene. The solvent was removed under reduced pressure to afford the title compound **4** (0.45 g, 46%) as an orange oil; δ_H (200 MHz, $CDCl_3$) 3.92 (3H, s, OMe), 6.83 (2H, d, J=1.2 Hz, H-5, H-6), 7.12 (1H, t, J=1.2 Hz, H-3). The NMR data was in agreement with the literature values.[21]

3.1.3. 2-Carbomethoxy-1,4-naphthoquinone 5. A mixture of methyl 1,4-dihydroxynaphthalene-2-carboxylate[22] (0.5 g, 2.29 mmol) and anhydrous sodium sulfate (2.0 g) in ethyl acetate (30 mL) was stirred with activated manganese dioxide (2.9 g, 34.4 mmol) at room temperature for 30 min. The suspension was filtered through Celite and the filter cake was washed with ethyl acetate. The solvent was removed under reduced pressure to afford the title compound **5** (0.25 g, 51%) as an orange solid. This material was satisfactory for use in the subsequent step without further purification; δ_H (200 MHz, $CDCl_3$) 3.81 (3H, s, OMe), 7.28 (1H, s, H-3), 7.82–8.16 (4H, m, H-5, H-6, H-7, H-8). The ^1H NMR data was in agreement with that reported in the literature.[22]

3.1.4. 2-Acetyl-1,4-benzoquinone 6. A mixture of 2,5-dihydroxyacetophenone (0.75 g, 4.9 mmol) and anhydrous sodium sulfate (1.25 g) in dry toluene (60.0 mL) was stirred with silver(I) oxide (5.6 g, 24.2 mmol) for 21 h. The suspension was filtered through sodium sulfate and Celite and the filter cake was washed with toluene. The solvent was removed under reduced pressure to afford orange crystals which were recrystallised from ether to afford the title compound **6** (0.51 g, 69%) as orange crystals, mp 63–65 °C (lit.[23] mp 64–65.5 °C); δ_H (200 MHz, $CDCl_3$) 2.57 (3H, s, Me), 6.83 (2H, apparent d, H-5, H-6), 7.01 (1H, t, J=1.8 Hz, H-3).

3.1.5. 2-Acetyl-1,4-naphthoquinone 7. 2-Acetyl-1,4-dimethoxynaphthalene[26] (40 mg, 0.17 mmol) and freshly prepared silver(II) oxide (340 mg, 2.78 mmol) were mixed in 1,4-dioxane (1.5 mL). To the mixture was added HNO_3 (0.46 mL, 6 mol L^{-1}) and the reaction stirred for 10 min. The reaction mixture was then quenched with H_2O (4 mL) and extracted with dichloromethane (4×8 mL). The organic layer was collected, washed with H_2O (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the title compound **7** (35 mg, 99%) as an orange solid, mp 81–83 °C (lit.[24] mp 80–84 °C).

3.1.6. 3-Acetyl-5-methoxy-1,4-naphthoquinone 8. A solution of ceric ammonium nitrate (470 mg, 0.86 mmol) in water (2.8 mL) was added dropwise to a solution of 3-acetyl-1,5-dimethoxy-4-naphthol[25] (85 mg, 0.34 mmol) in acetonitrile (7.2 mL). After stirring for 5 min, the mixture was diluted with dichloromethane (30 mL), washed with water (3×20 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give the title compound **8** (76.6 mg, 97%) as a yellow-orange solid, mp 102–104 °C (lit.[24] mp 101–105 °C).

3.1.7. *tert*-Butyl (3a*S,8b*S**)-8-methoxycarbonyl-7-hydroxy-2-oxo-2,3,3a,8b-tetrahydro-1*H*-[1]benzofuro[3,2-*b*]pyrrole-1-carboxylate 9.** To an ice-cooled solution of 2-methoxycarbonyl-1,4-benzoquinone 4 (200 mg, 1.2 mmol) dissolved in acetonitrile (8 mL) was added a solution of TBSOP 3 (700 mg, 2.36 mmol) in acetonitrile (12 mL) dropwise under nitrogen. After stirring for 2 h, the solution was warmed to room temperature then stirred for 18 h. The solvent was removed under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate (gradient elution 9:1 to 4:6) as eluent to afford the title compound **9** (150 mg, 36%) as colourless crystals, mp 114–116 °C, (Found: M^+, 349.1159, $C_{17}H_{19}NO_7$ requires 349.1161); ν_{max} (film)/cm^{-1} 3295v (OH), 2984m, 1754m (C=O), 1728m (C=O), 1683m (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, ^tBu), 2.94 (2H, apparent d, J=5.1 Hz, H-3), 3.95 (3H, s, OMe), 5.14 (1H, t, $J_{3a,8b}$=5.1 Hz, $J_{3a,3}$=5.1 Hz, H-3a), 5.81 (1H, d, $J_{3a,8b}$=5.1 Hz, H-8b), 6.93 (2H, apparent s, H-5, H-6), 9.65 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_3, C*Me*$_3$), 38.0 (CH_2, C-3), 52.1 (CH_3, OMe), 64.2 (CH, C-8b), 79.3 (CH, C-3a), 83.7 (C, *C*Me$_3$), 112.7 (C, C-8), 116.5 (CH, C-6), 119.9 (CH, C-5), 123.7 (C, C-8a), 150.2 (C, C-7), 154.0 (C, C-4a), 154.4 (C, NCO_2), 170.1 (C, C-2), 170.3 (C, CO_2Me); *m*/*z* 349 (M^+, 4%), 276 (M−O^{t}Bu, 3), 249 (70), 217 (100).

3.1.8. *tert*-Butyl (3a*S,10b*S**)-10-carbomethoxy-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]pyrrole-1-carboxylate 10.** To an ice-cooled solution of 2-carbomethoxy-1,4-naphthoquinone **5** (110 mg, 0.509 mmol) in acetonitrile (7 mL) was added a solution of TBSOP **3** (300 mg, 1.02 mmol) in acetonitrile (6 mL) dropwise under nitrogen. After stirring for 1 h, the solution was warmed to room temperature then stirred overnight. The solvent was removed under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate (7:3) as eluent to afford the title compound **10** (110 mg, 54%) as a red solid, mp >300 °C decomp., (Found: M^+, 399.1316, $C_{21}H_{21}NO_7$ requires 399.1316); ν_{max} (film)/cm^{-1} 3053m (OH), 2986m, 1750m (C=O), 1729m (C=O), 1265s (C–O); δ_H (300 MHz,

$CDCl_3$) 1.41 (9H, s, ^{t}Bu), 3.04 (2H, apparent d, J=5.4 Hz, H-3), 3.99 (3H, s, OMe), 5.28 (1H, t, J=5.4 Hz, H-3a), 5.93 (1H, d, J=5.4 Hz, H-10b), 7.59 (2H, m, H-6 and H-7), 7.89 (1H, m, H-5), 8.59 (1H, m, H-8), 11.09 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 27.8 (CH_3, C*Me*$_3$), 38.1 (CH_2, C-3), 52.0 (CH_3, OMe), 65.7 (CH, C-10b), 79.4 (CH, C-3a), 83.5 (C, *C*Me$_3$), 105.1 (C, C-10), 114.5 (C, C-10a), 121.7 (CH, C-5), 123.5 (C, C-4b), 124.3 (C, C-8a), 126.2 (CH, C-7), 129.0 (CH, C-6), 150.2 (C, C-4a), 150.3 (C, NCO_2), 154.0 (C, C-9), 179.5 (C, C-2), 171.2 (C, CO_2Me); *m*/*z* 399 (M^+, 3%), 326 (M−O^{t}Bu, 1), 299 (62), 267 (100).

3.1.9. *tert*-Butyl 2-(2-acetyl-1,4-dihydroxy-3-phenyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate 11. To an ice-cooled solution of 2-acetyl-1,4-benzoquinone **6** (200 mg, 1.33 mmol) dissolved in acetonitrile (6 mL) was added a solution of TBSOP **3** (790 mg, 2.66 mmol) in acetonitrile (14 mL) dropwise with stirring under nitrogen. After 20 h the solvent was removed under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate as eluent (gradient elution 9:1 to 1:9) to afford the title compound **11** (334 mg, 56%) as yellow crystals, mp 94–97 °C, (Found: M^+, 447.2076, $C_{22}H_{33}NO_6Si$ requires 447.2077); ν_{max} (film)/cm^{-1} 3338v (OH), 2929m, 1763m (NC=O), 1621m (C=O), 1290m (Si–C); δ_H (400 MHz, $CDCl_3$) 0.25 (6H, s, Si*Me*$_2^t$Bu), 1.01 (9H, s, SiMe$_2^t$Bu), 1.20 (9H, s, ^{t}Bu), 2.03 (3H, s, COMe), 4.30 (1H, s, OH), 5.46 (1H, d, J=3.6 Hz, H-4), 6.00 (1H, d, J=3.6 Hz, H-3), 6.92 (1H, d, J=8.9 Hz, H-6′), 7.08 (1H, d, J=8.9 Hz, H-5′), 11.69 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) −5.1 (CH_3, Si*Me*Me^{t}Bu), −4.9 (CH_3, SiMe*Me* ^{t}Bu), 18.1 (C, *C*Me$_3$), 25.5 (CH_3, SiMe$_2^t$Bu), 28.0 (CH_3, CO*Me*), 29.3 (CH_3, C*Me*$_3$), 92.6 (CH, C-4), 112.9 (CH, C-3), 116.8 (C, C-2), 119.0 (CH, C-6′), 120.4 (C, C-5), 121.1 (C, C-3′), 121.3 (C, C-2′), 122.7 (CH, C-5′), 145.7 (C, C-4′), 147.4 (C, C-1′), 155.5 (C, N*C*O$_2$), 205.9 (C, *C*OMe); *m*/*z* 447 (M^+, 11%), 391 (M−C_4H_8, 5), 347 (M−$C_4H_8CO_2$, 100), 316 (M−^{t}BuMe$_2$SiO, 20), 73 (O^{t}Bu, 90), 57 (C_4H_6, 62).

3.1.10. *tert*-Butyl 2-(3-acetyl-1,4-dihydroxy-2-naphthyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate 12. To an ice-cooled solution of 2-acetyl-1,4-naphthoquinone **7** (16 mg, 0.08 mmol) in acetonitrile (1.5 mL) was added a solution of TBSOP **3** (47 mg, 0.16 mmol) in acetonitrile (1.5 mL) dropwise under nitrogen atmosphere. After 1 h, the mixture was warmed to room temperature and then left stirred overnight. The solvent was evaporated under reduced pressure to afford a brown residue that was purified by flash chromatography using hexane–ethyl acetate (95:5) as eluent to give the title compound **12** (25 mg, 64%) as a yellow oil, (Found: M^+, 497.2231, $C_{27}H_{35}NO_6Si$ requires 497.2234); ν_{max} (film)/cm^{-1} 3485v (OH), 2930m, 1754m (C=O), 1675m (C=O); δ_H (200 MHz, $CDCl_3$) 0.28 (6H, s, Si*Me*$_2^t$Bu), 1.02 (9H, s, SiMe$_2^t$Bu), 1.04 (9H, s, ^{t}Bu), 2.08 (3H, s, Me), 5.50 (1H, d, J=3.5 Hz, H-4), 6.14 (1H, d, J=3.5 Hz, H-3), 7.54–7.77 (2H, m, H-6′, H-7′), 8.18 (1H, d, J=8.0 Hz, H-5′), 8.48 (1H, d, J=7.7 Hz, H-8′); δ_C (50 MHz, $CDCl_3$) −4.9 (CH_3, $SiMe_2$), −4.8 (CH_3, SiMe2), 18.3 (C, Si*C*Me$_3$), 25.6 (CH3, SiC*Me*$_3$), 27.1 (CH_3, Me), 28.9 (CH_3, C*Me*$_3$), 84.0 (C, *C*Me$_3$), 92.6 (CH, C-4), 113.0 (CH, C-3), 114.5 (C, C-5), 117.0 (C, C-2), 119.4 (CH, C-8′), 122.6 (CH, C-5′), 124.5 (CH, C-6′), 126.9 (CH, C-7′), 127.8 (C, C-4a′), 143.3 (C, C-1′), 145.9 (C, C-4′), 157.4 (C, NCO), 205.4 (C, *C*OMe). Three quaternary carbons (C-2′, C-3′ and C-8a′) were not observed; *m*/*z* 497 (M^+, 12%), 366 (M−^{t}BuMe$_2$SiO, 33), 73 (O^{t}Bu, 100), 57 (C_4H_6, 46).

3.1.11. *tert*-Butyl 2-(3-acetyl-5-methoxy-1,4-dihydroxy-2-naphthyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-pyrrole-1-carboxylate 13. To an ice-cooled solution of 2-acetyl-8-methoxy-1,4-naphthoquinone **8** (30 mg, 0.156 mmol) in acetonitrile (2 mL) was added a solution of TBSOP **3** (78 mg, 0.313 mmol) in acetonitrile (1.5 mL) dropwise under nitrogen. After 1 h, the solution was warmed to room temperature then stirred overnight. The solvent was removed under reduced pressure to afford a brown residue which was purified by flash chromatography using hexane–ethyl acetate (4:1) as eluent to afford the title compound **13** (26 mg, 38%) as a yellow oil, (Found: M^+, 527.2334, $C_{28}H_{37}NO_7Si$ requires 527.2339); δ_H (300 MHz, $CDCl_3$) 0.27 (6H, d, J=1.6 Hz, *Me*$_2^t$BuSi), 1.01 (9H, s, Me$_2^t$BuSi), 1.10 (9H, s, ^{t}Bu), 2.22 (3H, s, COMe), 4.06 (3H, s, OMe), 5.41 (1H, d, J=3.5 Hz, H-4), 5.58 (1H, s, OH), 6.04 (1H, d, J=3.5 Hz, H-3), 6.91 (1H, d, J=8.0 Hz, H-6′), 7.45 (1H, t, J=8.0 Hz, H-7′), 7.82 (1H, d, J=8.0 Hz, H-8′), 11.32 (1H, s, OH); *m*/*z* 527 (M^+, 10%), 366 (M−^{t}BuMe$_2$SiO, 36), 73 (O^{t}Bu, 100), 57 (C_4H_6, 41).

3.1.12. *tert*-Butyl (3a*S,10b*S**)-10-acetyl-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]pyrrole-1-carboxylate 14.** To a solution of 2-acetyl-1,4-naphthoquinone **7** (30 mg, 0.15 mmol) in anhydrous dichloromethane (4 mL) was added Eu(fod)$_3$ (158 mg, 0.15 mmol) and the mixture was stirred under nitrogen at room temperature for 50 min. The mixture was then cooled to −78 °C and a solution of TBSOP **3** (43 mg, 0.15 mmol) in anhydrous dichloromethane (2 mL) was added dropwise. The mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with H_2O (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a red–brown oil that was purified by flash chromatography with hexane–ethyl acetate (9:1 then 8:2 then 1:1) as eluent to give the title compound **14** (19 mg, 33%) as a yellow oil, (Found: M^+, 383.1371, $C_{21}H_{21}NO_6$ requires 383.1369); ν_{max} (film)/cm^{-1} 3445br (OH), 1773m (C=O), 1714m (C=O); δ_H (300 MHz, $CDCl_3$) 1.38 (9H, s, ^{t}Bu), 2.83 (3H, s, CO*Me*), 3.02 (1H, dd, J=18.0, 5.1 Hz, H-3A), 3.13 (1H, d, J=18 Hz, H-3B), 5.34 (1H, t, J=5.1 Hz, H-3a), 5.84 (1H, d, J=5.1 Hz, H-10b), 7.57 (1H, ddd, J=7.5, 7.5, 1.5 Hz, H-7), 7.63 (1H, ddd, J=7.5, 7.5, 1.5 Hz, H-6), 7.89 (1H, ddd, J=7.5, 1.5, 0.6 Hz, H-5), 8.40 (1H, ddd, J=7.5, 1.5, 0.6 Hz, H-8), 12.99 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 27.7 (CH_3, C*Me*$_3$) 31.5 (CH_3, CO*Me*), 38.3 (CH_2, C-3), 66.2 (CH, C-10b), 78.3 (CH, C-3a), 83.0 (C, *C*Me$_3$), 84.0 (C, C-10), 113.2 (C, C-10a), 121.9 (CH, C-5), 123.9 (C, C-8a), 124.9 (CH, C-8), 127.0 (C, C-4b), 127.5 (CH, C-7), 129.6 (CH, C-6), 149.5 (C, C-4a), 150.6 (C, NCO_2), 155.1 (C, C-9), 169.1 (C, C-2), 204.1 (C, *C*OMe); *m*/*z* (EI) 383 (M^+, 3%), 310 (M−O^{t}Bu, 3), 283 (M−^{t}Bu–COMe, 66), 239 (M−CO_2^tBu–COMe, 70), 73 (O^{t}Bu, 100). Silyloxypyrrole **12** (32 mg, 43%) was also recovered from the reaction.

3.1.13. *tert*-Butyl (3a*S,10b*S**)-10-acetyl-9-hydroxy-8-methoxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphtho-furo[3,2-*b*]pyrrole-1-carboxylate 15.** To a solution of 2-acetyl-8-methoxy-1,4-naphthoquinone **8** (36 mg, 0.16 mmol) in anhydrous dichloromethane (4 mL) was added $Eu(fod)_3$ (160 mg, 0.16 mmol) and the mixture was stirred under nitrogen at room temperature for 50 min. The mixture was then cooled to −78 °C and a solution of TBSOP **3** (46 mg, 0.16 mmol) in anhydrous dichloromethane (2 mL) was added dropwise. The mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with H_2O (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to give a red–brown oil that was purified by flash chromatography with hexane–ethyl acetate (9:1 then 8:2 then 1:1) as eluent to give the title compound **15** (24 mg, 38%) as a yellow oil, (Found: M^+, 413.1464, $C_{22}H_{23}NO_7$ requires 413.1475); ν_{max} (film)/cm^{-1} 3399b (OH), 1753m (C=O), 1638s (C=O), 1265s (C–O); δ_H (300 MHz, $CDCl_3$) 1.47 (9H, s, ^{t}Bu), 2.78 (3H, s, Me), 2.96–3.14 (2H, m, H-3), 4.09 (3H, s, OMe), 5.29 (1H, t, *J*=5.4 Hz, H-3a), 5.87 (1H, d, *J*=5.4 Hz, H-10b), 6.91 (1H, d, *J*=7.7 Hz, H-7), 7.43 (1H, t, *J*=7.7 Hz, H-6), 7.54 (1H, d, *J*=7.7 Hz, H-5), 9.73 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 29.0 (CH_3, C*Me*$_3$), 31.9 (CH_3, COMe), 38.3 (CH_2, C-3), 56.3 (CH_3, OMe), 63.5 (CH, C-10b), 79.4 (CH, C-3a), 83.5 (C, *C*Me_3), 106.5 (CH, C-7), 115.9 (CH, C-5), 115.9 (C, C-10a), 117.9 (C, C-8a), 121.1 (C, C-10), 123.5 (C, C-4b), 127.7 (CH, C-6), 148.3 (C, C-8), 150.3 (C, C-4a), 150.4 (C, NCO_2), 156.9 (C, C-8), 170.4 (C, C-2), 202.8 (C, COMe); *m*/*z* 413 (M^+, 4%), 340 (M−O^{t}Bu, 2), 73 (O^{t}Bu, 100). Silyloxypyrrole **12** (31 mg, 42%) was also recovered from the reaction.

3.1.14. *tert*-Butyl (3a*R,5*S**,11b*R**)-3,3a,5,11b-tetrahydro-5-hydroxy-7-methoxy-5-methyl-1*H*-[1]naphtho[2,3-*c*]pyran-2,6,11-trione-pyrrole-1-carboxylate 16.** To a solution of pyrrolidinonaphthofuran **15** (15 mg, 0.035 mmol) in acetonitrile (1.5 mL) was added dropwise a solution of ceric ammonium nitrate (39 mg, 0.07 mmol) in H_2O (1 mL) and the mixture stirred vigorously at 0 °C for 10 min. The reaction mixture was diluted with dichloromethane (5 mL) and H_2O (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic extracts were washed with H_2O (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a yellow oil that was purified by flash chromatography using hexane–ethyl acetate (4:6) as eluent. Further purification by flash chromatography using hexane–ethyl acetate (8:2, then 7:3, then 1:1) afforded the title compound **16** (12 mg, 75%) as a yellow oil; (Found: MH^+, 430.1503, $C_{22}H_{24}NO_8$ requires 430.1502); ν_{max} (film)/cm^{-1} 3434br (OH), 1663m (C=O), 1262m (C–O); δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, ^{t}Bu), 1.73 (3H, s, Me), 2.67 (1H, d, *J*=17.2 Hz, H-3A), 2.81 (1H, dd, *J*=4.0, 17.2 Hz, H-3B), 4.03 (4H, s, OH and OMe), 4.52 (1H, dd, *J*=4.0, 2.4 Hz, H-3a), 5.06 (1H, d, *J*=2.4 Hz, H-11b), 7.32 (1H, dd, *J*=8.1, 1.5 Hz, H-8), 7.71–7.78 (2H, m, H-9, H-10); δ_C (100 MHz, $CDCl_3$) 27.9 (CH_3, C*Me*$_3$), 28.3 (CH_3, Me), 39.8 (CH_2, C-3), 50.0 (CH, C-11b), 56.5 (CH_3, OMe), 65.6 (CH, C-3a), 83.8 (C, CMe_3), 93.8 (C, C-5), 117.7 (CH, C-8), 119.5 (CH, C-10), 120.1 (C, *C*OCMe_3), 134.6 (C, C-10a), 135.6 (CH, C-9), 136.3 (C, C-11a), 143.8 (C, C-5a), 150.5 (C, C-6a), 159.6 (C, C-7), 171.5 (C, C-2), 183.5 (C, C-11), 184.5 (C, C-6); *m*/*z* (CI) 430 (MH^+, 1%), 154 (100), 136 (67).

Acknowledgements

Financial assistance from The University of Auckland Research Committee is gratefully acknowledged.

References and notes

1. For a recent review on the vinylogous aldol reaction see: Casiraghi, G.; Zanardi, F. *Chem. Rev.* **2000**, *100*, 1929.
2. For a recent review on the vinylogous Mannich reaction see: Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.
3. For reviews on the synthetic utility of these 2-silyloxy dienes see: (a) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Chem. Soc. Rev.* **2000**, *29*, 109. (b) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607. (c) Casiraghi, G.; Rassu, G.; Zanardi, F.; Battistini, L. *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI: Stanford, 1998; Vol. 3, p 113.
4. Zanardi, F.; Battistini, L.; Rassu, G.; Auzzas, L.; Pinna, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 2048.
5. Pichon, M.; Jullian, J.-C.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1998**, *39*, 1755.
6. Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquottit, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307.
7. Rassu, G.; Carta, P.; Pinna, L.; Battistini, L.; Zanardi, F.; Acquottit, D.; Casiraghi, G. *Eur. J. Org. Chem.* **1999**, 1395.
8. Zanardi, F.; Battistini, L.; Nespi, M.; Rassu, G.; Spanu, P.; Cornia, M.; Casiraghi, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1167.
9. Spanu, P.; Rassu, G.; Ulgheri, F.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Tetrahedron* **1996**, *52*, 4829.
10. Rassu, G.; Zanardi, F.; Batistini, L.; Casiraghi, G. *Tetrahedron: Asymmetry* **1995**, *6*, 371.
11. (a) Brimble, M. A.; Duncalf, L. J.; Reid, D. C. W. *Tetrahedron: Asymmetry* **1995**, *6*, 263. (b) Brimble, M. A.; Elliot, R. J. *Tetrahedron* **1997**, *53*, 7715. (c) Brimble, M. A.; McEwan, J. F.; Turner, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1257.
12. (a) Brimble, M. A.; Stuart, S. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 881. (b) Brimble, M. A. *Pure Appl. Chem.* **2000**, *72*, 1635.
13. For a review on the isolation and biological activity of pyranonaphthoquinone antibiotics see: Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rev.* **1999**, *16*, 267.
14. For a preliminary communication of this work see: Brimble, M. A.; Halim, R.; Petersson, M. *Tetrahedron Lett.* **2002**, *43*, 4777.
15. (a) Cheng, J.; Burhart, A.; Derecskei-Kovacs, A.; Burgess, K. *J. Org. Chem.* **2000**, *65*, 900. (b) Cheng, J.; Reibenspies, J.; Derecskei-Kovacs, A.; Burgess, K. J. *Chem. Commun.* **1999**, 2501.
16. Anderton, N.; Cockrum, P.; Peter, A.; Colegate, S. M.; Edgard, J. A.; Flower, K.; Gardner, D.; Willing, R. I. *Phytochemistry* **1999**, *51*, 153.

17. Marcos, I.; Redero, E.; Bermejo, F. *Tetrahedron Lett.* **2000**, *41*, 8451.
18. Aroyo, Y.; de Paz, M.; Rodriguez, J. F.; Sanz-Tejedor, M. A.; Garcia Ruano, J. L. *J. Org. Chem.* **2002**, *67*, 5638.
19. Kuser, P.; Frauenfelder, E.; Eugster, C. H. *Helv. Chim. Acta* **1971**, *54*, 969.
20. Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760.
21. Schleusener, E.; Eugster, C. H. *Helv. Chim. Acta* **1972**, *55*, 986.
22. Brimble, M.; Spicer, J. A. *Aust. J. Chem.* **1991**, *44*, 197.
23. Kloetzel, M.; Dayton, R. P.; Abadir, B. Y. *J. Org. Chem.* **1955**, *20*, 38.
24. Read, G.; Ruiz, V. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 235.
25. Uno, H. *J. Org. Chem.* **1986**, *51*, 35.
26. Maruyama, M.; Kozuka, T. *Bull. Chem. Soc. Jpn* **1978**, *51*, 3586.
27. Rassu, G.; Zanardi, F.; Battistini, L.; Gaetani, E.; Casiraghi, G. *J. Med. Chem.* **1997**, *40*, 168.
28. Forest, J.; Petrow, V. *J. Chem. Soc.* **1950**, *3*, 2340.