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Tetrahedron 62 (2006) 3021–3027

Addition of 2-*tert*-butyldimethylsilyloxythiophene to activated quinones: an approach to thia analogues of kalafungin

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Received 1 November 2005; revised 21 December 2005; accepted 12 January 2006

Available online 2 February 2006

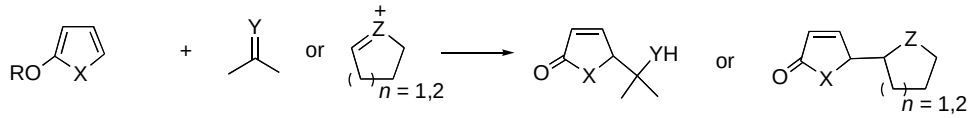
Abstract—The uncatalyzed reaction of 2-*tert*-butyldimethylsilyloxythiophene **2** with 1,4-quinones bearing either an electron withdrawing acetyl or a carbomethoxy group at C-2, was investigated. No reaction was observed using 1,4-quinones **8** and **9** bearing an ester group at C-2 whereas use of 1,4-quinones **10** and **11** bearing an acetyl group at C-2 only provided low yields of the silyloxythiophenes **15** and **16** resulting from electrophilic substitution of the silyloxythiophene by the 1,4-quinone. Use of the Lewis acids $InCl_3$, $Cu(OTf)_2$ and $BF_3 \cdot Et_2O$ were investigated in an effort to improve the yield of the desired annulation reaction. $BF_3 \cdot Et_2O$ proved to be the optimum catalyst for the synthesis of thiolactone naphthofuran adducts **14** and **18** from 1,4-naphthoquinones **9** and **11**, respectively. Reaction of 2-*tert*-butyldimethylsilyloxythiophene **2** with 1,4-benzoquinones **8** and **10** bearing a carbomethoxy or an acetyl group at C-2, respectively, afforded thiolactone benzofuran adducts **13** and **17**, respectively, catalyzed by either $InCl_3$ or $Cu(OTf)_2$. Addition of 2-*tert*-butyldimethylsilyloxythiophene **2** to 3-acetyl-5-methoxy-1,4-naphthoquinone **12** afforded adduct **19** that underwent oxidative rearrangement to thiolactone pyranonaphthoquinone **20** using ceric ammonium nitrate in acetonitrile, thus providing a novel approach for the synthesis of a thia 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]

We have studied the reaction of the silyl enolate d^4 synthons, TMSOF **1** and TBSOP **3** with 1,4-benzoquinones and 1,4-naphthoquinones bearing electron withdrawing groups at C-2 in which initial conjugate addition to the quinone is followed by intramolecular cyclization to afford either a furobenzofuran or pyrrolobenzofuran or a furonaphthofuran or pyrrolonaphthofuran, respectively (Scheme 2). This annulation step formed a key step in our synthesis of the pyranonaphthoquinone antibiotic kalafungin[11] and the synthesis of aza analogues[12] thereof, by effecting a facile oxidative cyclization of the initial annulation product.

As an extension to this work, we now herein report the results of our studies on the hitherto unreported addition of



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: Silyloxythiophene; Quinones; Pyranonaphthoquinone antibiotics; Annulation.
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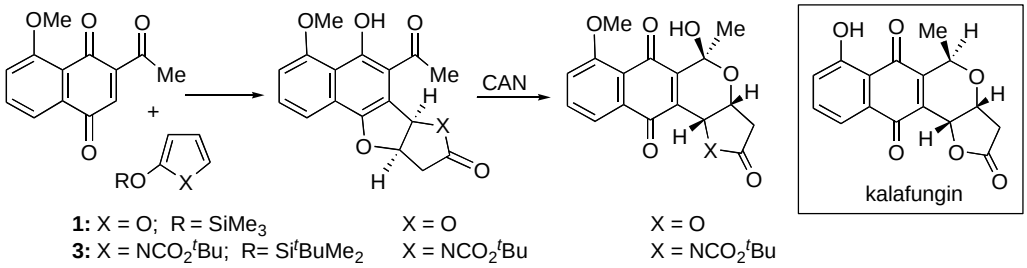
doi:10.1016/j.tet.2006.01.040



Scheme 2.

2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** to a series of benzoquinones and naphthoquinones bearing either an acetyl group or a carbomethoxy group at C-2. The resultant annulation products would provide access to thia analogues of the kalafungin skeleton that were of interest due to their potential bioactivity as bioreductive alkylating agents.[13]

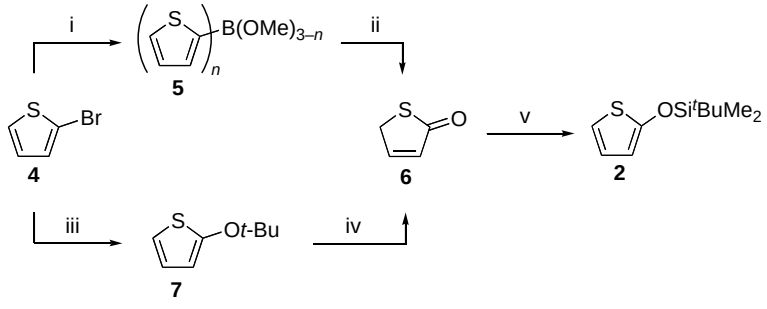
2. Results and discussion

It was proposed that addition of 2-(*tert*-butyldimethylsilyloxy)thiophene (TBSOT) **2** to 1,4-quinones bearing an electron withdrawing group at C-2 would follow a similar pathway to the addition of TMSOF **1** and TBSOP **3** affording thia analogues of the corresponding furo[3,2-*b*]-benzofuran and furo[3,2-*b*]naphthofuran adducts. Initial synthesis of TBSOT **2** was therefore required.

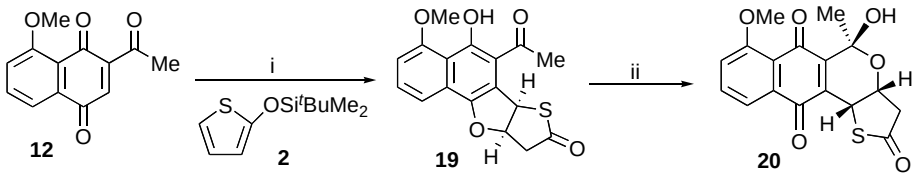
It was envisaged that TBSOT **2** could be prepared from thiolactone **6** using the procedure reported by Casiraghi et al.[14] (Scheme 3). The thiolactone precursor **6** was originally prepared by Hawkins[15] from 2-bromothiophene **4** via the boronate ester **5**. Following the procedure of Hawkins[15] 2-bromothiophene **4** was treated with *n*-butyllithium followed by trimethylborate. Oxidative work-up of the resultant boronate **5**, however, furnished thiolactone **6** in only 26% yield. Frisell and Lawesson[16] reported an alternative procedure for the preparation of thiolactone **6** employing *tert*-butyl ether **7**. Accordingly, the Grignard generated from 2-bromothiophene **4** was treated with *tert*-butyl peroxybenzoate and the resultant *tert*-butyl ether **7** hydrolyzed with *p*-toluenesulfonic acid at 160 °C. Gratifyingly, thiolactone **6** was isolated in 61% yield. Silyl enol ether formation[14] using *tert*-butyldimethylsilyl trifluoromethane sulfonate and 2,6-lutidine proceeded smoothly to furnish TBSOT **2** in 84% yield.

With TBSOT **2** in hand, the conjugate addition reactions to several readily accessible quinones **8**, **9**, **10**, **11**, similar in structure to the quinone precursor **12** required to prepare a thia analogue of kalafungin (Scheme 4), were next investigated (Table 1). Our previous paper describing the addition of silyloxypyrrole **3** to activated quinones reports the syntheses of the quinone starting materials.[12]

It was anticipated that the uncatalyzed addition of TBSOT **2** to 2-carbomethoxyquinones **8** and **9** would provide thiolactone adducts **13** and **14**, respectively. However, after stirring the quinones **8** and **9** with TBSOT **2** at room temperature in acetonitrile for 16 h, no reaction was observed (Table 1). Treatment of the more electron withdrawing 2-acetylquinones **10** and **11** with TBSOT **2** was more encouraging, providing substituted silyloxythiophenes **15** and **16**, arising from direct eletrophilic aromatic

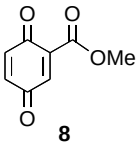
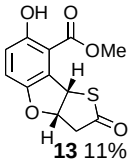
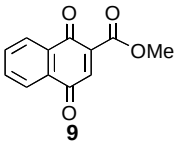
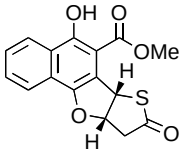
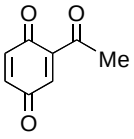
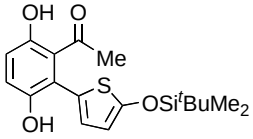
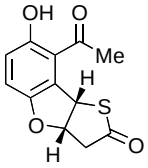
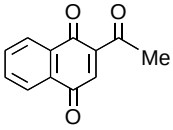
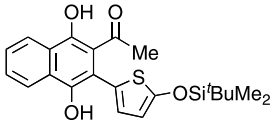
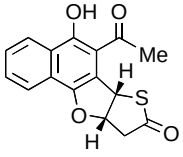


Scheme 3. Reagents and conditions: (i) *n*-BuLi, THF, reflux 1 h then $B(OMe)_3$, 60 °C, 2 h; (ii) H_2O_2, 0 °C to rt, 26% over two steps; (iii) Mg, Et_2O, rt, 3 h, reflux, 0.5 h then $PhCO_2O^tBu$, 0 °C, 12 h; (iv) *p*-TsOH, 160 °C, 10 min, 61% over two steps; (v) $^tBuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 1 h, 84%.



Scheme 4. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 1 h, 45%; (ii) CAN (2.0 equiv), MeCN–H_2O (1:1), 21%.

Table 1. Addition of TBSOT **2** to 1,4-quinones **8**, **9**, **10** and **11**

Quinone	Uncatalyzed[a]	$InCl_3$[b]	$Cu(OTf)_2$[c]	$BF_3 \cdot OEt_2$[d]
 **8**	No reaction	 **13** 11%	**13** 13%	—
 **9**	No reaction	 **14** 27%	**14** 30%	**14** 31%
 **10**	 **15** 35%	 **17** 35%	**17** 22%	—
 **11**	 **16** 11%	 **18** 9%	**18** 33%	**18** 48%

[a] Reactions carried out using **2** (1.1 equiv) in acetonitrile at rt for 16 h.
[b] Reactions carried out using **2** (1.0 equiv) $InCl_3$ (5%) in acetonitrile at rt, 0 °C then rt, 16 h.
[c] Reactions carried out using **2** (1.0 equiv), $Cu(OTf)_2$ (1.0 equiv) in dichloromethane, −78 °C then rt, 2 h.
[d] Reactions carried out using **2** (1.0 equiv), $BF_3 \cdot Et_2O$ (1.1 equiv) in dichloromethane, −78 °C then rt, 1 h.

substitution of the thiophene ring, in 35 and 11% yield, respectively.

Whilst the uncatalyzed addition of TBSOT **2** to the aforementioned quinones **8**, **9**, **10** and **11** failed to furnish the desired thiolactone adducts **13**, **14**, **17** and **18**, it was hoped that use of a Lewis acid to promote the desired annulation reaction would be more fruitful. Yadav et al.[17,18,19,20] and Loh and Wei[21,22] have reported the catalysis of conjugate addition reactions using indium(III) chloride, however, neither group had investigated the use of 2-silyloxythiophenes as nucleophiles or quinones as Michael acceptors. Accordingly, quinones **8**, **9**, **10** and **11** were treated with TBSOT **2** in the presence of indium(III) chloride (5 mol%) in acetonitile at 0 °C. After allowing the reaction mixture to warm to room temperature and stirring for 16 h gratifyingly, the desired corresponding thiolactone adducts **13**, **14**, **17** and **18** were isolated in modest yield after purification by flash chromatography.

In an effort to improve the yields of the desired adducts **13**, **14**, **17** and **18**, the use of an alternative Lewis acid was next investigated. Brimble et al.[23] have employed copper(II) trifluoromethanesulfonate as a Lewis acid in the Michael addition of TMSOF **1** to various chiral naphthoquinones. Following this precedent, a solution of each of the quinones **8**, **9**, **10** and **11** in dichloromethane was added to a suspension of copper(II) trifluoromethanesulfonate (1.0 equiv) in dichloromethane at −78 °C and the resultant mixture then treated with TBSOT **2**. Although the reactions proceeded cleanly to completion, as monitored by thin-layer chromatography, it was nevertheless disappointing to observe no significant improvement in the isolated yields of the desired adducts **13**, **14**, **17** and **18**.

The desired adducts were highly susceptible to degradation upon flash chromatography presumably accounting for the low yields of the isolated products. Efforts to try to improve the stability of the adducts via protection of the free phenol as either an acetate or a *tert*-butyldimethylsilyl ether were unsuccessful, and led only to the formation of a complex mixture of products in both instances. Use of reverse phase HPLC and alumina or florisil as solid supports for chromatography also did not offer any improvement.

Catalysis of the conjugate addition reaction using boron trifluoride etherate was next investigated. Accordingly, a solution of each of the quinones **8**, **9**, **10** and **11** and TBSOT **2** in dichloromethane at −78 °C was treated with boron trifluoride etherate (1.1 equiv). The reaction of benzoquinones **8** and **10** led to the formation of a complex mixture of products, whilst naphthoquinones **9** and **11** afforded thiolactone naphthofurans **14** and **18** in 31 and 48% yield, respectively; possibly reflecting the lower reactivity of the naphthoquinones **9** and **11** compared to the corresponding benzoquinones **8** and **10**.

Having successfully prepared thiolactone naphthofuran **18** in a modest 48% yield using boron trifluoride etherate as a Lewis acid, the synthesis of a thia analogue of kalafungin was next undertaken (Scheme 4). Following the procedure established for the preparation of **18**, a solution of naphthoquinone **12** and TBSOT **2** in dichloromethane at −78 °C was treated with boron trifluoride etherate (1.1 equiv) affording thiolactone naphthofuran **19** in 45% yield. Facile oxidative cyclization of **19** to the desired thiolactone pyranonaphthoquinone **20** using ceric ammonium nitrate proceeded in 21% yield. Use of alternative oxidants was unsuccessful affording none of the desired oxidative cyclization product. Disappointingly, the thia analogue **20** of kalafungin thus prepared was unstable rapidly degrading to a complex mixture of products.

3. Conclusions

In summary, a study of the addition of TBSOT **2** to several electron deficient quinones is reported. Uncatalyzed addition of TBSOP **2** to 1,4-quinones **8** and **9** bearing carbomethoxy substituents at C-2 was unsuccessful whilst use of the 2-acetylquinones **10** and **11** afforded the electrophilic substitution products **15** and **16**, respectively. Use of the Lewis acids $InCl_3$, $Cu(OTf)_2$ and $BF_3 \cdot Et_2O$ to promote the annulation reaction afforded the desired thiolactone adducts **13**, **14**, **17** and **18**. $BF_3 \cdot Et_2O$ proved to be the optimum catalyst for the reaction of TBSOT **2** with the naphthoquinones **9** and **11** to provide adducts **14** and **18**, respectively, whilst $InCl_3$ and $Cu(OTf)_2$ were more effective for the reaction of TBSOT **2** with the benzoquinones **9** and **11** to provide adducts **13** and **17**, respectively. These thiolactone benzofuran and naphthofuran adducts provide novel heterocyclic ring systems that can be further elaborated to provide thia analogues of natural products as demonstrated by the conversion of adduct **19** to a thia analogue **20** of the bioreductive alkylating agent kalafungin.

4. Experimental

4.1. General details

All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere using standard syringe and septum techniques unless otherwise stated. Diethyl ether and tetrahydrofuran were freshly distilled from sodium/benzophenone. Hexane, pentane, dichloromethane, triethylamine and diethylamine were distilled from calcium hydride. Thin-layer chromatography was performed on precoated 0.2 mm Merck Kieselgel 60 F_{254} silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Flash column chromatography was performed using Reidel-de Häen Kieselgel or Merck Kieselgel 60 F (both 230–400 mesh) with the indicated solvents. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer Spectrum One Fourier Transform IR spectrophotometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained using either a Bruker DRX-400 spectrophotometer operating at either 400 or 100 MHz or a Bruker Avance 300 spectrometer operating at 300 or 75 MHz, respectively. Data are expressed in parts per million downfield shift from tetramethylsilane as an internal standard or relative to $CDCl_3$. All J values are given in Hertz. Assignments are made with the aid of DEPT 135, COSY and HSQC experiments. High-resolution mass spectra were recorded using a VG70-SE spectrometer operating at a nominal accelerating voltage of 70 eV. Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Quinones **8**, **9**, **10** and **11** were prepared as described in our previous paper.[12]

4.2. Preparation of 2-(*tert*-butyldimethylsilyloxy) thiophene 2

4.2.1. 3-Thiolen-2-one 6. *Procedure A*. In an adaptation of the procedure used by Hawkins,[15] 2-bromothiophene **4** (2.00 mL, 20.7 mmol) was dissolved in dry tetrahydrofuran (25 mL) at room temperature under an atmosphere of nitrogen. To this stirred solution was added *n*-butyllithium (15.2 mL, 22.7 mmol, 1.50 M) dropwise slowly over 20 min. The resultant solution was heated at reflux for 1 h, cooled to 45 °C then trimethylborate (1.6 mL, 13.8 mmol) added via syringe. After heating for 2 h at 60 °C the reaction was cooled to 0 °C. Water (5 mL) was added followed by hydrogen peroxide (4.9 mL, 161.1 mmol) dropwise and the solution allowed to warm to room temperature. After 2 h the mixture was acidified and extracted with diethyl ether (3×50 mL). The combined organic extracts were dried over magnesium sulphate, filtered and the solvent removed at reduced pressure. Purification by flash column chromatography using hexane–ethyl acetate (8/2) as eluent provided the title compound **6** (538 mg, 26%) as a yellow oil; δ_H (300 MHz, $CDCl_3$) 4.15 (2H, dd, J=2.7, 2.0 Hz, H5), 6.43 (1H, dt, J=5.9, 2.0 Hz, H3) and 7.58 (1H, dt, J=5.9, 2.7 Hz, H4). This data was in agreement with that reported in the literature.[24]

Procedure B. In an adaptation of the procedure used by Frisell and Lawesson,[16] a two-necked flask was charged with magnesium turnings (527 mg, 21.7 mmol) and a single crystal of iodine then covered with dry diethyl ether (40 mL). To this stirred mixture was added 10% of a solution of 2-bromothiophene **4** (2.0 mL, 20.7 mmol) in diethyl ether (70 mL). After gently heating the mixture to initiate a reaction the remainder of the 2-bromothiophene solution was then added dropwise. The mixture was stirred for 3 h at room temperature then 0.5 h under reflux before cooling to 0 °C in an ice-bath. *tert*-Butylperoxy benzoate (3.3 cm^3, 17.6 mmol) was added dropwise and the mixture allowed to warm to room temperature. After 12 h the mixture was poured into ice-water (30 mL) and acidified with concentrated hydrochloric acid. The aqueous layer was extracted with diethyl ether (3×100 mL) and the combined extracts dried over magnesium sulphate. Filtration and removal of the solvent afforded a crude oil that was purified by flash column chromatography using hexane as eluent. The resultant 2-*tert*-butoxythiophene **7** was treated with *p*-toluenesulfonic acid (10 mg) and heated at 160 °C for 10 min. Purification by flash column chromatography using hexane–ethyl acetate (8/2) as eluent gave the title compound

6 (1.26 g, 61%) as a yellow oil. The spectroscopic data was identical to that reported above and was in agreement with that reported in the literature.[24]

4.2.2. 2-(*tert*-Butyldimethylsilyloxy)thiophene 2. Following the procedure reported by Casiraghi et al.[14] 3-thiolen-2-one **6** (1.25 g, 12.5 mmol) was dissolved in dichloromethane (25 mL) under an atmosphere of nitrogen and the solution cooled to 0 °C. To this stirred solution was added 2,6-lutidine (4.4 mL, 37.4 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.30 mL, 18.7 mmol). The mixture was allowed to warm to room temperature, stirred for 1 h then the solvent was removed under reduced pressure. Purification of the resultant residue by flash column chromatography using hexane as eluent provided the title compound **2** (2.24 g, 84%) as a colourless oil; δ_H (300 MHz, $CDCl_3$) 0.22 (6H, s, $^tBuMe_2Si$), 0.98 (9H, s, $^tBuMe_2Si$), 6.14 (1H, dd, $J=3.1$, 1.6 Hz, H3), 6.50 (1H, dd, $J=5.9$, 1.6 Hz, H5), 6.65 (1H, dd, $J=5.9$, 3.1 Hz, H4). This data was in agreement with that reported in the literature.[14]

4.3. Addition of 2-(*tert*-butyldimethylsilyloxy)thiophene 2 to quinones

4.3.1. Representative experimental procedures. *A. Uncatalyzed conjugate addition*. To a stirred solution of quinone (0.10 mmol) in acetonitrile (15 mL) at 0 °C under an atmosphere of nitrogen was added a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (24 mg, 0.11 mmol) in acetonitrile (6 mL). The mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed at reduced pressure and the resultant residue purified by flash column chromatography to afford the title compound.

B. Indium(III) chloride catalyzed conjugate addition. To a suspension of indium(III) chloride (11 mg, 0.05 mmol) in acetonitrile (2 cm^3) at 0 °C under an atmosphere of nitrogen was added a solution of quinone (1.00 mmol) in acetonitrile (3 mL) followed by a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (236 mg, 1.10 mmol) in acetonitrile (3 mL). The mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed at reduced pressure and the resultant residue purified by flash column chromatography to afford the title compound.

C. Copper(II) trifluoromethane sulfonate catalyzed conjugate addition. To a stirred suspension of copper(II) trifluoromethanesulfonate (362 mg, 1.00 mmol) in dichloromethane (2 mL) at −78 °C under an atmosphere of nitrogen was added a solution of quinone (1.00 mmol) in dichloromethane (3 mL) followed by a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (214 mg, 1.00 mmol) in dichloromethane (3 mL). After stirring for 2 h, the mixture was allowed to warm to room temperature then filtered through a pad of Celite®. The solvent was removed at reduced pressure and the resultant residue purified by flash column chromatography to afford the title compound.

D. Boron trifluoride etherate catalyzed conjugate addition. To a stirred solution of quinone (1.00 mmol) in dichloromethane (5 mL) at −78 °C under an atmosphere of nitrogen was added a solution of 2-(*tert*-butyldimethylsilyloxy)thiophene **2** (214 mg, 1.00 mmol) in dichloromethane (5 mL). Boron trifluoride etherate (0.14 mL, 1.10 mmol) was added dropwise and the mixture stirred for 1 h. The reaction was quenched by the addition of water (3 cm^3) and allowed to warm to room temperature. The aqueous layer was extracted with dichloromethane (3×15 mL) and the combined organic extracts dried over magnesium sulphate. Filtration and removal of the solvent at reduced pressure gave a residue that was purified by flash column chromatography to afford the title compound.

4.3.2. *cis*-8-Carbomethoxy-7-hydroxy-2-oxo-2,3,3a,8b-tetrahydro-1*H*-[1]benzofuro[3,2-*b*]thiophene 13. Flash column chromatography using hexane–ethyl acetate (8/2) as the eluent gave the title compound **13** (Procedure B 11%; Procedure C 13%) as a red solid; mp 160–162 °C; ν_{max}(film)/cm^{-1} 3426br (OH) and 1644s (CO); δ_H (400 MHz, $CDCl_3$), 3.12 (1H, dd, $J=18.2$, 6.2 Hz, H3), 3.23 (1H, d, $J=18.2$ Hz, H3), 3.98 (3H, s, Me), 5.31 (1H, t, $J=6.2$ Hz, H3a), 5.76 (1H, d, $J=6.2$ Hz, H8b), 6.92 (1H, d, $J=8.9$ Hz, H6), 7.03 (1H, d, $J=8.9$ Hz, H5) and 10.44 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 47.8 (CH_2, C3), 52.6 (CH_3, Me), 56.2 (CH, C8b), 83.2 (CH, C3a), 108.5 (quat., C8), 118.2 (CH, C6), 119.4 (CH, C5), 127.4 (quat., C8a), 152.3 (quat., C7), 157.1 (quat., C4a), 169.3 (quat., CO) and 204.4 (quat., C2); *m/z* (EI): 266 (M^+, 100), 234 (M−CH_3OH, 78), 224 (M−CH_2CO), 207 (M−CO_2Me, 2), 192 (M−CH_2SCO, 16) and 57 (C_4H_9, 14); HRMS (EI): Found M^+, 266.0239. $C_{12}H_{10}O_5S$ requires 266.0249.

4.3.3. *cis*-10-Carbomethoxy-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]thiophene 14. Flash column chromatography using hexane–ethyl acetate (7/3) as the eluent gave the title compound **14** (Procedure B 27%; Procedure C 30%; Procedure D 31%) as pale yellow needles; mp 221–223 °C; ν_{max}(film)/cm^{-1} 3376br (OH), 1697s (CO), 1665s (CO) and 1233s; δ_H (400 MHz, $CHCl_3$) 3.22 (1H, dd, $J=18.4$, 6.3 Hz, H3), 3.37 (1H, d, $J=18.4$ Hz, H3), 4.00 (3H, s, OMe), 5.46 (1H, t, $J=6.3$ Hz, H3a), 5.91 (1H, d, $J=6.3$ Hz, H10b), 7.58 (1H, t, $J=7.7$ Hz, H7), 7.66 (1H, t, $J=7.7$ Hz, H6), 7.90 (1H, d, $J=7.7$ Hz, H5), 8.40 (1H, d, $J=7.7$ Hz, H8) and 11.83 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 48.0 (CH_2, C3), 52.5 (CH_3, OMe), 57.8 (CH, C10b), 83.2 (CH, C3a), 101.5 (quat., C10), 117.3 (quat., C10a), 121.7 (CH, C5), 124.2 (quat., C8a), 125.6 (quat., C4b), 127.0 (CH, C7), 129.9 (CH, C6), 148.3 (quat., C9), 157.3 (quat., C4a), 170.5 (quat., CO_2Me) and 204.9 (quat., C2); *m/z* (FAB): 316 (M^+, 42%) and 89 (100); HRMS (FAB): Found M^+, 316.04008. $C_{16}H_{12}O_3S$ requires 316.04055.

4.3.4. 2-(2-Acetyl-1,4-dihydroxy-3-phenyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-thiophene 15. Flash column chromatography using hexane−ethyl acetate (7/3) as the eluent gave the title compound **15** (Procedure A 35%) as a pale yellow oil; ν_{max}(film)/cm^{-1} 3384br (OH) and 1635s (CO); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, $^tBuMe_2Si$), 1.00 (9H, s, $^tBuMe_2Si$), 2.12 (3H, s, Me), 5.28 (1H, s, OH), 6.26 (1H, d, $J=3.7$ Hz, H4), 6.69 (1H, d, $J=3.7$ Hz, H3), 6.98 (1H, d, $J=9.0$ Hz, H6′), 7.13 (1H, d, $J=9.0$ Hz, H5′) and 11.36 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) −5.0 (CH_3, $^tBuMe_2Si$), 18.2 (quat., $^tBuMe_2Si$), 20.9 (CH_3, $^tBuMe_2Si$), 60.3 (CH_3, Me), 110.3 (CH, C4), 119.8 (quat., C2′), 119.8

(CH, C6′), 122.2 (quat., C3′), 122.2 (quat., C2), 122.7 (CH, C5′), 127.8 (CH, C3), 147.2 (quat., C4′), 155.1 (quat., C1′), 171.1 (quat., C5) and 205.8 (quat., CO); *m/z* (EI): 364 (M^+, 66%), 349 (M−Me, 2), 307 (M−C_4H_9, 6), 233 (12), 115 (6) and 43 (18); HRMS (EI): Found M^+, 364.11671. $C_{18}H_{24}O_4SSi$ requires 364.11646.

4.3.5. 2-(2-Acetyl-1,4-dihydroxy-3-naphthyl)-5-(*tert*-butyldimethylsilyloxy)-1*H*-thiophene 16. Flash column chromatography using hexane–ethyl acetate (8/2) as the eluent gave the title compound **16** (Procedure A 11%) as a yellow oil; ν_{max}(film)/cm^{-1} 3434br (OH) and 1675s (CO); δ_H (400 MHz, $CDCl_3$) 0.29 (6H, s, ^{t}Bu*Me*$_2$Si), 1.00 (9H, s, ^{t}*Bu*Me$_2$Si), 2.19 (3H, s, Me), 5.85 (1H, s, OH), 6.29 (1H, d, *J*=3.6 Hz, H4), 6.78 (1H, d, *J*=3.6 Hz, H3), 7.60 (1H, ddd, *J*=7.6, 7.6, 1.2 Hz, H7′), 7.69 (1H, ddd, *J*=7.6, 7.6, 1.2 Hz, H6′), 8.20 (1H, d, *J*=7.6 Hz, H5′), 8.47 (1H, d, *J*=7.6 Hz, H8′) and 13.82 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) −4.9 (CH_3, ^{t}Bu*Me*$_2$Si), 18.3 (quat., ^{t}*Bu*Me$_2$Si), 25.5 (CH_3, ^{t}*Bu*Me$_2$Si), 30.1 (CH_3, Me), 109.0 (quat., C2′), 109.5 (CH, C4), 114.7 (quat., C3′), 122.6 (CH, C5′), 123.5 (quat., C2), 124.6 (CH, C8′), 126.2 (quat., C4a′), 127.2 (CH, C3), 127.6 (CH, C7′), 130.1 (CH, C6′), 130.9 (quat., C8a′), 143.3 (quat., C4′), 156.9 (quat., C1′), 163.7 (quat., C5) and 205.3 (quat., CO); *m/z* (EI): 414 (M^+, 78), 399 (M−Me, 3), 371 (M−COMe, 7), 282 (12), 115 (9) and 43 (17); HRMS (EI): Found M^+, 414.13198. $C_{22}H_{26}O_4SSi$ requires 414.13211.

4.3.6. *cis*-8-Acetyl-7-hydroxy-2-oxo-2,3,3a,8b-tetrahydro-1*H*-[1]benzofuro[3,2-*b*]thiophene 17. Flash column chromatography using hexane–ethyl acetate (7/3) as the eluent gave the title compound **17** (Procedure B 35%; Procedure C 22%) as a pale-yellow solid; mp 125–127 °C (degradation); ν_{max}(film)/cm^{-1} 3376br (OH), 1716s (CO), 1637s (CO), 1472 and 1210; δ_H (400 MHz, $CHCl_3$) 2.68 (3H, s, Me), 3.13 (1H, dd, *J*=18.2, 5.6 Hz, H3), 3.30 (1H, d, *J*=18.2 Hz, H3), 5.31 (1H, t, *J*=5.6 Hz, H3a), 5.70 (1H, d, *J*=5.6 Hz, H8b), 6.94 (1H, d, *J*=9.0 Hz, H6), 7.07 (1H, d, *J*=9.0 Hz, H5) and 12.25 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 31.2 (CH_3, Me), 47.3 (CH_2, C3), 56.6 (CH, C8b), 83.2 (CH, C3a), 116.1 (quat., C8), 119.4 (CH, C5), 120.8 (CH, C6), 126.2 (quat., C8a), 152.5 (quat., C7), 158.7 (quat., C4a) 202.4 (quat., CO_2Me or C2) and 202.5 (quat., CO_2Me or C2); *m/z* (EI): 250 (M^+, 100%), 208 (37), 189 (44), 175 (27), 152 (18), 147 (18), 137 (28) and 43 (49); HRMS (EI): Found M^+, 250.03021. $C_{12}H_{10}O_4S$ requires 250.02998.

4.3.7. *cis*-10-Acetyl-9-hydroxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]thiophene 18. Flash column chromatography using hexane–ethyl acetate (1/1) as the eluent gave the title compound **18** (Procedure B 9%; Procedure C 33%; Procedure D 48%) as orange needles; mp 210–212 °C; ν_{max}(film)/cm^{-1} 3345br (OH), 1677s (CO) and 1593s (CO); δ_H (400 MHz, $CDCl_3$) 2.74 (3H, s, Me), 3.26 (1H, dd, *J*=18.3, 5.7 Hz, H3), 3.43 (1H, d, *J*=18.3 Hz, H3), 5.48 (1H, dd, *J*=5.7, 6.4 Hz, H3a), 5.87 (1H, d, *J*=6.4 Hz, H10b), 7.58 (1H, ddd, *J*=7.6, 7.6, 1.1 Hz, H7), 7.70 (1H, ddd, *J*=7.6, 7.6, 1.1 Hz, H6), 7.92 (1H, d, *J*=7.6 Hz, H5), 8.48 (1H, d, *J*=7.6 Hz, H8) and 14.56 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 30.7 (CH_3, Me), 47.5 (CH_2, C3), 58.2 (CH, C10b), 83.1 (CH, C3a), 109.5 (quat., C10a), 116.3 (quat., C10), 121.6 (CH, C5), 124.3 (quat., C8a), 124.8 (CH, C8), 125.4 (quat., C4b), 126.4 (CH, C7), 130.7 (CH, C6), 133.4 (quat., C9), 160.3 (quat., C4a), 202.1 (quat., CO) and 202.8 (quat., C2); *m/z* (EI): 300 (M^+, 100), 257 (M−COMe, 2), 256 (4), 57 (7) and 43 (37); HRMS (EI): Found M^+, 300.04557. $C_{16}H_{12}O_4S$ requires 300.04563.

4.3.8. *cis*-10-Acetyl-9-hydroxy-8-methoxy-2-oxo-2,3,3a,10b-tetrahydro-1*H*-[1]naphthofuro[3,2-*b*]thiophene 19. Flash column chromatography using hexane–ethyl acetate (7/3) as the eluent gave the title compound **19** (Procedure D 45%) as a brown solid; mp 230–233 °C (degradation); ν_{max}(film)/cm^{-1} 3439br (OH), 1694s (CO), 1649, 1631, 1450, 1399, 1244, and 1229; δ_H (300 MHz, $CHCl_3$) 2.75 (3H, s, Me), 3.20 (1H, dd, *J*=18.2, 5.9 Hz, H3), 3.31 (1H, d, *J*=18.2 Hz, H3), 4.13 (3H, s, OMe), 5.39 (1H, t, *J*=5.9 Hz, H3a), 5.92 (1H, d, *J*=5.9 Hz, H10b), 6.92 (1H, d, *J*=8.0 Hz, H7), 7.49 (1H, t, *J*=8.0 Hz, H6), 7.55 (1H, dd, *J*=8.0, 1.0 Hz, H5) and 10.38 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 33.2 (CH_3, Me), 48.1 (CH_2, C3), 56.6 (CH_3, OMe), 57.1 (CH, C10b), 83.4 (CH, C3a), 106.5 (CH, C7), 115.5 (quat., C8), 115.7 (quat., C10a), 116.0 (CH, C5), 121.7 (quat., C10), 124.9 (quat., C4b), 129.1 (CH, C6), 148.2 (quat., C4a), 153.6 (quat., C9), 157.4 (quat., C8), 199.5 (quat., CO) and 205.8 (quat., C1); *m/z* (FAB): 331 (MH^+, 23%), 330 (M, 18), 120 (59) and 89 (100); HRMS (FAB): Found M^+, 330.05675. $C_{17}H_{14}O_5S$ requires 330.05620.

4.3.9. *cis*-(3a,5,9b)-3,3a,5,11b-Tetrahydro-5-hydroxy-7-methoxy-5-methyl-1*H*-[1]naptho[2,3-*c*]pyran-2,6,11-trione thiophene 20. To a stirred solution of thienylnaphthofuran **11** (40 mg, 0.12 mmol) in acetonitrile (2 cm^3) and water (2 cm^3) at 0 °C was added ceric ammonium nitrate (133 mg, 0.24 mmol). After stirring for 20 min, water (2 cm^3) was added and the aqueous layer extracted with dichloromethane (3×10 cm^3). The combined extracts were dried over magnesium sulphate, filtered and the solvent removed under reduced pressure. Purification of the resultant residue by flash column chromatography using hexane–ethyl acetate (8/2) as eluent gave the title compound **20** (9 mg, 21%) as an unstable red-brown oil that rapidly degraded to a complex mixture of products; δ_H (300 MHz, $CHCl_3$) 1.78 (3H, s, Me), 2.88 (1H, d, *J*=17.1 Hz, H3), 2.99 (1H, dd, *J*=17.1, 3.8 Hz, H3), 4.04 (3H, s, OMe), 4.87 (1H, t, *J*=3.8 Hz, 3a), 4.92 (1H, d, *J*=3.8 Hz, 11b), 7.34–7.38 (1H, m, H8), 7.70–7.78 (2H, m, H9 and H10).

Acknowledgements

The authors thank the University of Auckland for financial support of this work.

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