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Asymmetric Michael addition of 2-trimethylsilyloxyfuran to chiral naphthoquinones

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Abstract

Asymmetric Michael reactions of 1,4-naphthoquinones bearing a chiral auxiliary at C-2 **1–4** with 2-trimethylsilyloxyfuran using various Lewis acids afforded the corresponding furofuran adducts **5–12**. Moderate levels of diastereomeric excess were obtained using (*R*)-pantolactone, (*S*)-*N*-methyl-2-hydroxysuccinimide and (*R*)-(+)-4-benzyl-2-oxazolidinone as chiral auxiliaries. Low asymmetric induction was achieved using a camphorsultam auxiliary. X-Ray crystallographic analysis of the pantolactone adduct enabled determination of the absolute stereochemistry of all adducts obtained. Evidence that the TMS-furan addition occurs *via* a Michael reaction rather than a Diels–Alder cycloaddition is provided.

1. Introduction

The asymmetric addition of silyloxydienes to chiral 1,4-naphthoquinones is an area that is still largely unexplored. Moreover, there have been strong indications that conjugate addition competes with and sometimes dominates conventional Diels–Alder cycloaddition.[1] Stoodley et al.[2] obtained high levels of stereoinduction in the Diels–Alder addition of 5-hydroxy-1,4-naphthoquinone (juglone) bearing a carbohydrate chiral auxiliary to various dienes. Other efforts have concentrated on the use of chiral catalysts, such as that used by Yamamoto et al.[3] or the use of a chiral diene.[4]

The addition of 2-trimethylsilyloxyfuran (TMS-furan) to 1,4-naphthoquinones has played a key role in our synthetic effort directed towards the synthesis of various members of the pyranonaphthoquinone family of antibiotics. The resulting furonaphthofuran adducts undergo oxidative rearrangement upon treatment with ceric ammonium nitrate to afford the furonaphthopyran skeleton (Scheme 1). The pyranonaphthoquinone antibiotics kalafungin,[5] frenolicin[6] and the arizonins[7] have been prepared using

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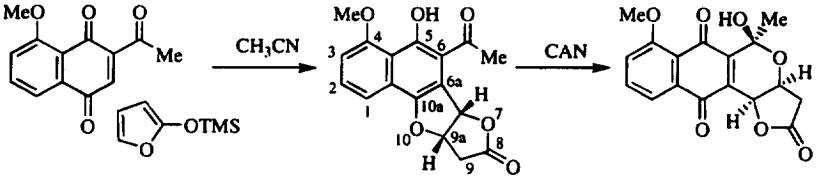
this methodology. A logical extension of this work is to achieve an asymmetric version of the key furofuran annulation.



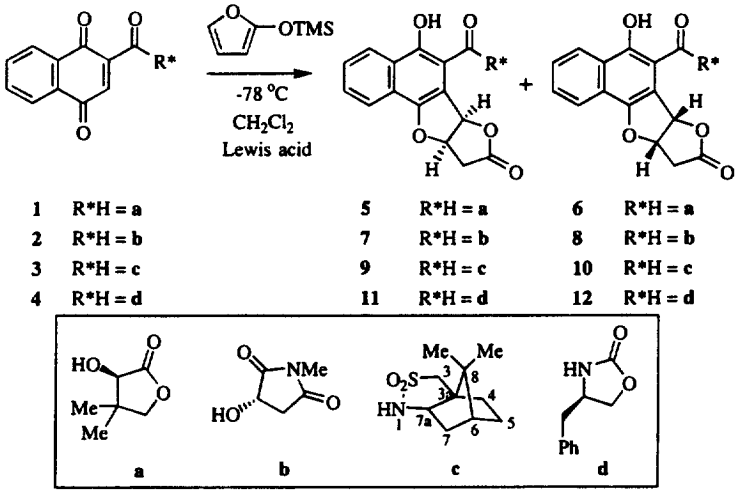
Scheme 1.

In an earlier paper we report only moderate stereoinduction in cycloadditions of naphthoquinones to various dienes using a variety of chiral catalysts.[8] A large number of ligand–Lewis acid catalysts were screened without obtaining the Diels–Alder adducts in significant enantiomeric excess. We therefore herein examine the use of a naphthoquinone bearing a chiral auxiliary at C-2, in an attempt to further develop the asymmetric addition of TMS-furan. Moderate levels of asymmetric induction have previously been reported in the addition of TMS-furan to a 1,4-benzoquinone bearing a chiral sulfoxide at C-2.[9]

2. Results and discussion

Based on strong precedent for the use of chiral auxiliaries attached to C-2 of 1,4-naphthoquinones to provide asymmetric induction in Diels–Alder reactions with cyclopentadiene,[10] the addition of 2-trimethylsilyloxyfuran to a range of chiral C-2 substituted 1,4-naphthoquinones was studied. The chiral auxiliaries on the quinones would be expected to provide a stereodirecting effect regardless of whether a Michael or a Diels–Alder pathway predominated.

Addition of 2-trimethylsilyloxyfuran to naphthoquinone **1**[10] bearing a pantolactone chiral auxiliary (**a**) at −78°C in the presence of a variety of Lewis acids afforded adducts **5** and **6** in moderate yield, which were separable by flash chromatography (Scheme 2). The optimum procedure involved the use of $Sn(OTf)_2$ which afforded adducts **5** and **6** (major) in 53% yield and in a ratio of 1:4.0 (Table 1).



Scheme 2.

X-Ray crystallography was employed to obtain the absolute stereochemistry of the more crystalline minor adduct **5**. An ORTEP[11] depiction of **5** is given in Fig. 1. In a related study of the addition

Table 1
Reaction of **1** with 2-trimethylsilyloxyfuran†

Lewis Acid	Yield 5 and 6 (%)	Ratio 6:5	D.e. (%)
–	51	1.6:1	24
$Cu(OTf)_2$	58	2.7:1	46
$ZnCl_2$	45	2.1:1	36
$Ti(O^iPr)_4$	32	1.9:1	32
$TiCl_2(O^iPr)_2$	32	1.8:1	28
$TiCl_4$	complex mixture		
$Sn(OTf)_2$	**53**	**4.0:1**	**60**
$BF_3.OEt_2$	60	2.8:1	48
$FeCl_3$	complex mixture		
$MgCl_2$	74	1.8:1	28

† Reactions were carried out in dichloromethane at −78 °C using 100 mol% Lewis acid.

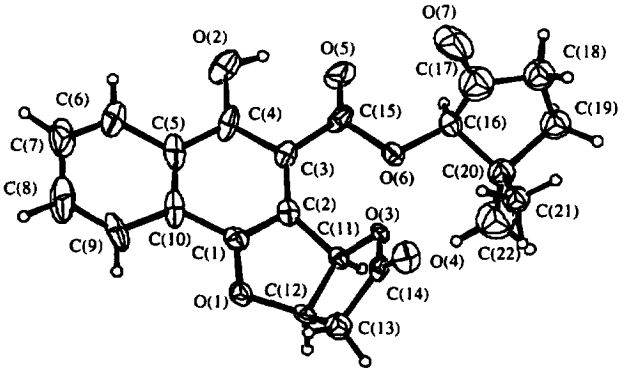
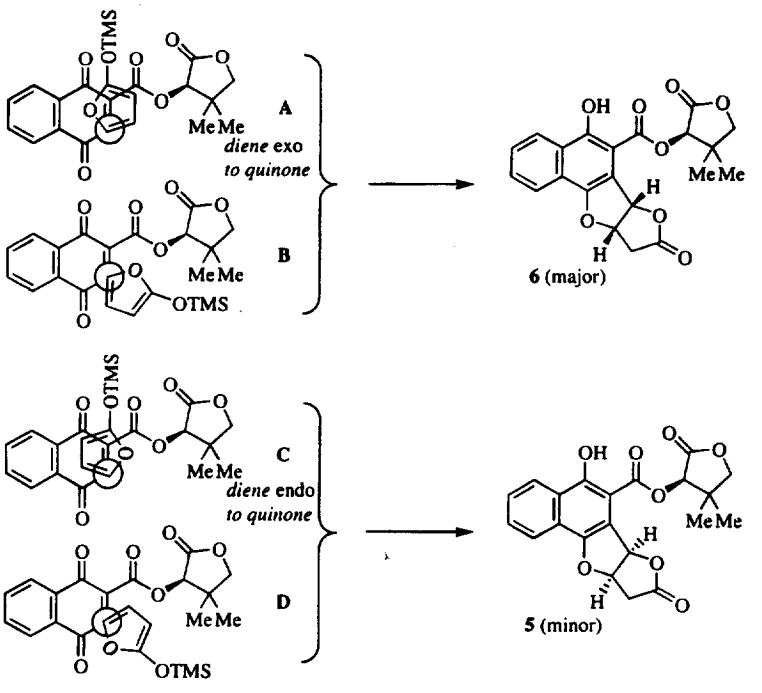


Fig. 1. Minor adduct **5**

of cyclopentadiene to quinone **1** the pantolactone ring shields the lower face of quinone **1** and the diene preferentially added to the top face with *endo* geometry.[10] In the present work, however, it was unclear whether TMS-furan addition occurred *via* a concerted Diels–Alder cycloaddition, or by a Michael addition.[9]

Given the two possible modes of addition (Diels–Alder versus Michael) there are four possible approaches of the diene to the top face of the quinone (Scheme 3). The regiochemistry of the addition is clear-cut and the related study using cyclopentadiene suggested that the major diastereomer forms from the diene adding to the top face of the quinone. *endo*-Addition of the diene to the top face of quinone **1** as in (**C**) would be preferred over *exo*-addition (**A**). However this approach (**C**) leads to the minor isomer **5** (Fig. 1). A Michael addition therefore provides a more likely rationale. In this case an antiperiplanar transition state (**B**) which leads to formation of the major adduct **6** is favoured over (**D**). This model has been used to account for the stereocontrol observed in Lewis acid catalysed additions to aldehydes and imines.[12] Therefore in the present work the Michael addition is the most plausible mechanism by which the annulation proceeds.

Addition of 2-trimethylsilyloxyfuran to quinone **2**[10] bearing the chiral auxiliary (*S*)-*N*-methyl-2-hydroxysuccinimide,[13] in the presence of various Lewis acids afforded adducts **7** (major) and **8** in



Scheme 3.

Table 2
Reaction of **2** with 2-trimethylsilyloxyfuran†

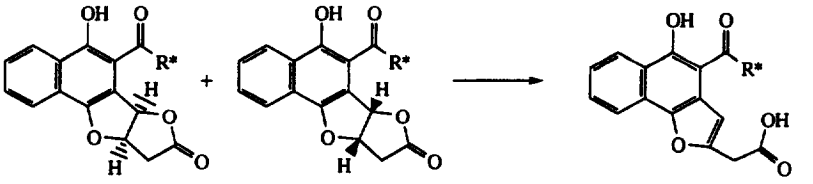
Lewis Acid	Yield 7 and 8 (%)	Ratio 7:8	D.e. (%)
–	50	2.1:1	36
$Cu(OTf)_2$	76	1.6:1	22
$ZnCl_2$	63	1.5:1	20
$Sn(OTf)_2$	**53**	**4.0:1**	**60**
$BF_3.OEt_2$	60	2.8:1	48

† Reactions were carried out in dichloromethane at –78 °C using 100 mol% Lewis acid.

moderate yield (Scheme 2), which were separable by flash chromatography. Again, the optimum result (Table 2) was achieved using $Sn(OTf)_2$ wherein **7** (major) and **8** were obtained in 53% yield and in a ratio of 4.0:1.

The similarity in the diastereoselectivity observed with both *Helmchen ligands*[14] **a** and **b** is not unexpected in that in related Diels–Alder reactions similar levels of asymmetric induction were observed with each ligand affording complementary adducts.[13] The TMS-furan adducts **7** and **8** were unstable and opened to acid **13**[15] on standing (Scheme 4).

Addition of 2-trimethylsilyloxyfuran to previously prepared quinone **3**,[10] bearing a camphorsultam auxiliary **c**, at −78°C in the presence of a variety of Lewis acids afforded adducts **9** (major) and **10** in high yield, which were separable by flash chromatography (Scheme 2). The optimum result was achieved using $ZnCl_2$ wherein **9** and **10** were obtained in 92% yield and in a ratio of 1.78:1 (Table 3). This level of asymmetric induction was much lower than that obtained using cyclopentadiene.[10] Adducts **9** and **10** were also unstable, forming **14** on standing (Scheme 4).



7 R*H = b
9 R*H = c
11 R*H = d

8 R*H = b
10 R*H = c
12 R*H = d

13 R*H = b
14 R*H = c
15 R*H = d

Scheme 4.

Table 3
Reaction of **3** with 2-trimethylsilyloxyfuran†

Lewis Acid	Yield 9 and 10 (%)	Ratio 9:10	D.e. (%)
–	20*	1.1:1	4
$Cu(OTf)_2$	60	1.1:1	6
$ZnCl_2$	**92**	**1.8:1**	**28**
$Sn(OTf)_2$	43	1.2:1	8
$BF_3.OEt_2$	hydroquinone recovered		–

† Reactions were carried out in dichloromethane at –78 °C using 100 mol% Lewis acid. * 21% hydroquinone also recovered.

Table 4
Reaction of **4** with 2-trimethylsilyloxyfuran†

Lewis Acid	Yield 11 and 12 (%)	Ratio 11:12	D.e. (%)
–	**56**	**4.9:1**	**66**
$Cu(OTf)_2$	57	1.5:1	20
$ZnCl_2$	73	2.0:1	34
$Sn(OTf)_2$	complex mixture		
$BF_3.OEt_2$	complex mixture		

† Reactions were carried out in dichloromethane at –78 °C using 100 mol% Lewis acid.

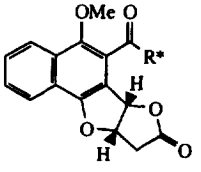
Addition of 2-trimethylsilyloxyfuran to quinone **4** (prepared from oxazolidinone **d**) at −78°C, in the presence of several Lewis acids, afforded adducts **11** (major) and **12**, which were separable by flash chromatography (Scheme 2). In this case the best diastereoselectivity was achieved in the absence of a Lewis acid wherein **11** and **12** were obtained in 56% yield and in a ratio of 4.88:1 (Table 4). When a Lewis acid is used, the molecular conformation of the complexed quinone **4** must be restricted such that both faces of the olefin are equally available for attack. In this case the Lewis acid free system, where there is less conformational rigidity, actually provides greater discrimination between the two faces of the quinone. The TMS-furan adducts **11** and **12** again proved to be unstable and readily underwent ring-opening in solution to acid **15** (Scheme 4).

2.1. Removal of auxiliaries

The auxiliaries were successfully removed from related cyclopentadiene adducts using reducing agents such as lithium borohydride.[10] These reducing agents would interfere with the lactone ring in the TMS-

furan adducts **5–12**, hence auxiliary removal in the present work was more problematic. Indeed, all efforts to remove pantolactone from **5–12** using $LiAlH_4$, $LiBH_4$ or DIBAL afforded only complex mixtures of extremely polar products.

Methylation of naphthol **6** with methyl iodide and silver(I) oxide to methyl ether **16** followed by hydrolysis or reduction using $LiBH_4$ also resulted in a complex mixture of products. Removal of the chiral auxiliaries using $LiBH_4$ was also attempted on the 4-benzyl-2-oxazolidinone **7**, camphorsultam **9** and 2-hydroxy-*N*-methylsuccinimide **11** adducts, however only a complex mixture of products was formed. $LiOH/H_2O_2$ removal[16] of the camphorsultam **c** was also unsuccessful in that the ring opened acid **14** was isolated in 68% yield (Scheme 4).



16 R*H=**a**

3. Conclusion

Addition of 2-trimethylsilyloxyfuran to 1,4-naphthoquinones **1–4** bearing a chiral auxiliary at C-2 resulted in moderate levels of stereoinduction. A d.e. of 66% was achieved using chiral oxazolidinone **d** as an auxiliary in the absence of a Lewis acid. X-Ray crystallographic analysis of the minor pantolactone adduct **5** indicates that the addition proceeds *via* a Michael addition and not a Diels–Alder cycloaddition. The sensitivity of the furonaphthofuran ring system, however, has prevented removal of the auxiliaries without adversely affecting the remainder of the molecule.

4. Experimental

4.1. General details

Melting points were determined using a Reichert Kofler block and are uncorrected. Infrared absorption spectra were recorded using a Perkin–Elmer 1600 Series FTIR spectrometer as Nujol mulls or thin films between sodium chloride plates. ^1H NMR and ^{13}C NMR spectra were obtained using either a Bruker AM 400 or a Bruker AC 200 spectrometer. ^{13}C NMR spectra were interpreted with the aid of DEPT 135 and DEPT 90 experiments. Low resolution mass spectra were recorded using a VG 70-SE spectrometer operating at an accelerating voltage of 70 eV. High resolution mass spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate, using EI, CI with ammonia or LSIMS with mnba. High resolution CI mass spectra were recorded at the University of Otago, Dunedin, New Zealand and LSIMS mass spectra were recorded at the Central Services Laboratory, Hobart, Australia. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) using hexane/ethyl acetate as eluent.

4.2. Representative Michael addition of 2-trimethylsilyloxyfuran to 1 using $ZnCl_2$

4.2.1. (+)-(3′R,6bR,9aR)- and (−)-(3′R,6bS,9aS)-Dihydro-4,4-dimethyl-2-oxo-3-furanyl 5-hydroxy-8-oxo-6b,8,9,9a-tetrahydrofuro[3,2-b]-naphtho[2,1-d]furan-6-carboxylate 5 and 6

To a solution of (3*R*)-dihydro-4,4-dimethyl-2-oxo-3-furanyl 1,4-dioxonaphthalene-2-carboxylate[10] (30 mg, 0.096 mmol) in dichloromethane (5 mL) cooled to −78°C, was added zinc chloride (96 μL of 1 M solution in CH_2Cl_2, 1.0 equiv.). The mixture was then treated with 2-trimethylsilyloxyfuran (20 μL), stirred for 1 h, then poured into 10% sodium hydrogen carbonate solution (4 mL) and extracted with dichloromethane (3×5 mL). The organic extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure. The residue was purified by flash chromatography (hexane:ethyl acetate, 2:1) to furnish adducts **6** and **5** in a 2.13:1 ratio (36% d.e.).

Adduct **5** was isolated as colourless platelets (5.4 mg, 14%): $[\alpha]_D$=+35.5 (*c*=0.45, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 3H, 4′-Me), 1.36 (s, 3H, 4′-Me), 3.12–3.20 (m, 2H, 9-CH_2), 4.09–4.21 (m, 2H, 5′-H_A and 5′-H_B), 5.43–5.57 (m, 1H, 9a-H), 5.62 (s, 1H, 3′-H), 6.48 (d, *J*=6.2 Hz, 1H, 6b-H), 7.67–7.74 (m, 2H, 2-H and 3-H), 7.96 (d, *J*=7.7 Hz, 1H, 1-H), 8.43 (d, *J*=8.0 Hz, 1H, 4-H), 11.45 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (CH_3, 4′-Me), 23.7 (CH_3, 4′-Me), 35.7 (CH_2, C-9), 40.4 (quat, C-4′), 76.4 (CH, C-3′), 77.1 (CH_2, C-5′), 81.3 (CH, C-9a), 85.8 (CH, C-6b), 100.8 (quat, C-6), 111.8 (quat, C-6a), 122.1 (CH, C-1 or C-4), 124.5 (quat, C-4a or C-10b), 125.0 (CH, C-4 or C-1), 126.9 (quat, C-10b or C-4a), 128.0 (CH, C-2 or C-3), 130.3 (CH, C-3 or C-2), 150.9 (quat, C-10a), 157.8 (quat, C-5), 168.8 (quat, ester), 171.0 (quat, C-2′), 174.3 (quat, C-8); IR (KBr) 1771 (lactone), 1739 (ester), 1663, 1599 (C=C), 1446, 1384, 1156 cm^{-1}; *m/z* (EI, %) 398 (M^+, 4), 268 ($C_{15}H_8O_5$, 61), 224 (57), 197 (77), 71 (89), 43 (100); HRMS analysis (EI, M^+) ($C_{21}H_{18}O_8$=398.1002) found *m/z* 398.1022.

Adduct **6** was isolated as a yellow oil (11.6 mg, 30%): $[\alpha]_D$=−8.6 (*c*=1.16, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (s, 3H, 4′-Me), 1.36 (s, 3H, 4′-Me), 3.08–3.17 (m, 2H, 9-CH_2), 4.08–4.25 (m, 2H, 5′-H_A and 5′-H_B), 5.44–5.57 (m, 1H, 9a-H), 5.70 (s, 1H, 3′-H), 6.52 (d, *J*=6.3 Hz, 1H, 6b-H), 7.62–7.76 (m, 2H, 2-H and 3-H), 7.94 (d, *J*=8.1 Hz, 1H, 1-H), 8.43 (d, *J*=7.6 Hz, 1H, 4-H), 11.67 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 (CH_3, 4′-Me), 23.2 (CH_3, 4′-Me), 35.7 (CH_2, C-9), 41.1 (quat, C-4′), 76.3 (CH, C-3′), 77.2 (CH_2, C-5′), 81.4 (CH, C-9a), 86.2 (CH, C-6b), 100.6 (quat, C-6), 111.8 (quat, C-6a), 122.1 (CH, C-1 or C-4), 124.6 (quat, C-4a or C-10b), 124.9 (CH, C-4 or C-1), 126.8 (quat, C-10b or C-4a), 127.9 (CH, C-2 or C-3), 130.4 (CH, C-3 or C-2), 150.9 (quat, C-10a), 158.2 (quat, C-5), 169.2 (quat, ester), 172.5 (quat, C-2′), 174.7 (quat, C-8); IR (film) 1776 (lactone), 1743 (ester), 1670, 1600 (C=C), 1388, 1229, 1154 cm^{-1}; *m/z* (EI, %) 398 (M^+, 15), 380 (35), 269 ($C_{15}H_9O_5$, 61), 223 (62), 198 (61), 71 (78), 43 (100); HRMS analysis (EI, M^+) ($C_{21}H_{18}O_8$=398.1002) found *m/z* 398.1003. For other Lewis acids see Table 1 in text.

4.2.2. (+)-(3′S,6bR,9aR)- and (−)-(3′S,6bS,9aS)-1-Methyl-2,5-dioxo-3-pyrrolidinyl 5-hydroxy-8-oxo-6b,8,9,9a-tetrahydrofuro[3,2-b]-naphtho[2,1-d]furan-6-carboxylate 7 and 8

Compounds **7** and **8** were prepared from quinone **2** (30 mg, 0.1 mmol) and TMS-furan (20 μL) using $ZnCl_2$ (0.1 mmol) by the procedure described above.

Adduct **7** was isolated as a colourless solid (9.1 mg, 38%): mp 192–194°C; $[\alpha]_D$=+32.9 (*c*=0.45, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.93 (dd, *J*=18.3, 5.2 Hz, 1H, 4′-H_B), 3.02–3.13 (m, 2H, 9-CH_2) 3.09 (s, 3H, N–Me), 3.38 (dd, *J*=18.3, 8.6 Hz, 1H, 4′-H_A), 5.42–5.52 (m, 1H, 9a-H), 5.86 (dd, *J*=8.6, 5.2 Hz, 1H, 3′-H), 6.45 (d, *J*=6.3 Hz, 1H, 6b-H), 7.58–7.73 (m, 2H, 2-H and 3-H), 7.92 (d, *J*=7.1 Hz, 1H, 1-H), 8.41 (d, *J*=7.6 Hz, 1H, 4-H), 11.49 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2 (CH_3, N–Me), 35.7 (CH_2, C-4′), 35.9 (CH_2, C-9), 68.2 (CH, C-3′), 81.2 (CH, C-9a), 86.3 (CH, C-6b), 100.5 (quat, C-6), 111.5 (quat, C-6a), 122.1 (CH, C-1 or C-4), 124.5 (quat, C-4a or C-10b), 124.9 (CH,

C-4 or C-1), 126.7 (quat, C-10b or C-4a), 128.0 (CH, C-2 or C-3), 130.4 (CH, C-3 or C-2), 150.4 (quat, C-10a), 158.1 (quat, C-5), 169.0 (quat, ester), 172.8 (quat, C-2′ or C-5′), 173.1 (quat, C-5′ or C-2′), 174.9 (quat, C-8); IR (KBr) 1773 (lactone), 1711 (amide), 1666, 1576 (C=C), 1439, 1381, 1229, 1161 cm^{-1}; *m/z* (EI, %) 397 (M^+, 15), 370 (6), 268 ($C_{15}H_8O_5$, 66), 223 (64), 197 (67), 139 (51), 44 (100); HRMS analysis (EI, M^+) ($C_{20}H_{15}O_8N$=397.0798) found *m/z* 397.0802.

Adduct **8** was also isolated as a colourless solid (6.1 mg, 25%): mp 186–188°C; $[\alpha]_D$=−24.0 (*c*=0.40, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 3.00 (dd, *J*=18.3, 5.2 Hz, 1H, 4′-H_B), 3.01–3.13 (m, 2H, 9-CH_2) 3.11 (s, 3H, N–Me), 3.32 (dd, *J*=18.3, 8.5 Hz, 1H, 4′-H_A), 5.42–5.56 (m, 1H, 9a-H), 5.85 (dd, *J*=8.5, 5.2 Hz, 1H, 3′-H), 6.46 (d, *J*=6.3 Hz, 1H, 6b-H), 7.60–7.78 (m, 2H, 2-H and 3-H), 7.94 (d, *J*=7.0 Hz, 1H, 1-H), 8.42 (d, *J*=7.6 Hz, 1H, 4-H), 11.34 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2 (CH_3, N–Me), 35.4 (CH_2, C-4′), 35.7 (CH_2, C-9), 69.6 (CH, C-3′), 81.2 (CH, C-9a), 86.2 (CH, C-6b), 100.6 (quat, C-6), 111.4 (quat, C-6a), 122.2 (CH, C-1 or C-4), 124.6 (quat, C-4a or C-10b), 125.0 (CH, C-4 or C-1), 126.8 (quat, C-10b or C-4a), 128.1 (CH, C-2 or C-3), 130.5 (CH, C-3 or C-2), 150.9 (quat, C-10a), 158.4 (quat, C-5), 169.2 (quat, ester), 172.8 (quat, C-2′ or C-5′), 173.0 (quat, C-5′ or C-2′), 174.7 (quat, C-8); IR (KBr) 1774 (lactone), 1710 (amide), 1439, 1387, 1285, 1167 cm^{-1}; *m/z* (EI, %) 397 (M^+, 15), 370 (6), 268 ($C_{15}H_8O_5$, 66), 223 (64), 197 (67), 187 (38), 139 (51), 44 (100); HRMS analysis (EI, M^+) ($C_{20}H_{15}O_8N$=397.0798) found *m/z* 397.0792. For other Lewis acids see Table 2 in text.

4.2.3. (−)-(3S)-1-Methyl-2,5-dioxo-3-pyrrolidinyl 2-carboxyethyl-5-hydroxynaphtho[1,2-b]furan-4-carboxylate ***13***

Both **7** and **8** proved to be highly unstable and opened to give acid **13** (yellow oil) on standing: $[\alpha]_D$=−10.0 (*c*=0.04, acetone); ^1H NMR (200 MHz, $CDCl_3$) δ 3.01 (s, 3H, N–Me), 3.15 (dd, *J*=18.0, 5.0 Hz, 1H, 4′-H_B), 3.42 (dd, *J*=18.0, 8.6 Hz, 1H, 4′-H_A), 3.97 (s, 2H, CH_2CO_2H), 6.05 (dd, *J*=8.6, 5.0 Hz, 1H, 3′-H), 7.23 (s, 1H, 3-H), 7.54–7.87 (m, 2H, 7-H and 8-H), 8.18 (d, *J*=7.0 Hz, 1H, 9-H), 8.42 (d, *J*=8.4 Hz, 1H, 6-H), 9.87 (s, 1H, COOH), 11.91 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1 (CH_3, N–Me), 34.6 (CH_2, C-4′), 36.4 (CH_2, CH_2CO_2H), 70.3 (CH, C-3′), 108.9 (quat, C-2), 108.9 (CH, C-3), 120.3 (CH, C-6 or C-9), 121.1 (quat, C-4 or C-3a), 121.8 (quat, C-3a or C-4), 123.0 (quat, C-5a or C-9a), 125.6 (CH, C-6 or C-9), (C-9a or C-5a obscured), 126.1 (CH, C-7 or C-8), 131.6 (CH, C-7 or C-8), 152.9 (quat, C-9b), 155.3 (quat, C-5), 170.2 (quat, ester), 171.3 (quat, COOH), 174.3 (quat, C-5′), 174.3 (quat, C-2′); IR (KBr) 1710 (amide and acid), 1440, 1382, 1285, 1229 cm^{-1}; *m/z* (EI, %) 397 (M^+, 19), 367 (38), 353 ($M-CO_2$, 44), 268 (65), 238 (78), 224 (79), 197 (48), 139 (55), 45 (100); HRMS analysis (EI, M^+) ($C_{20}H_{15}O_8N$=397.0798) found *m/z* 397.0803.

4.2.4. (−)-[3aS-(3aα,6α,7aβ),6b′R,9a′R]- and (−)-[3aS-(3aα,6α,7aβ),6b′S,9a′S]-Hexahydro-8,8-dimethyl-1-[5′-hydroxy-8′-oxo-6b′,8′,9′,9a′-tetrahydrofuro[3,2-b]naphtho[2,1-d]furan-6′-oyl]-3H-3a,6-methano-2,1-benzisothiazole-2,2-dioxide ***9*** *and* ***10***

Compounds **9** and **10** were prepared from quinone **3** (40 mg, 0.1 mmol) and TMS-furan (20 μL) using $ZnCl_2$ (1 equiv.) by the procedure described above.

Adduct **9** was isolated as a colourless oil (28 mg, 59%): $[\alpha]_D$=−27.4 (*c*=1.1, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 3H, 8-Me_A), 1.29 (s, 3H, 8-Me_B), 1.28–2.28 (m, 7H, 6-CH, 7-CH_2, 4-CH_2 and 5-CH_2), 3.01–3.18 (m, 2H, 9′-CH_2), 3.40–3.59 (m, 2H, 3-H_A and 3-H_B), 4.21–4.37 (m, 1H, 7a-H), 5.58 (ddd, *J*=6.1, 2.5, 6.1 Hz, 1H, 9a′-H), 6.69 (d, *J*=6.1 Hz, 1H, 6b′-H), 7.57–7.72 (m, 2H, 2′-H and 3′-H), 7.91 (d, *J*=7.1 Hz, 1H, 1′-H), 8.36 (d, *J*=7.3 Hz, 1H, 4′-H), 9.37 (bs, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9 (CH_3, 8-Me_A), 20.5 (CH_3, 8-Me_B), 26.6 (CH_2, C-5), 33.0 (CH_2, C-4), 35.7 (CH_2, C-9′), 37.8 (CH_2, C-7), 44.6 (CH, C-6), 47.8 (quat, C-8), 47.8 (quat, C-3a), 53.4 (CH_2, C-3), 65.4 (CH, C-7a), 80.9 (CH, C-9a′), 85.7 (CH, C-6b′), 103.6 (quat, C-6′), 113.1 (quat, C-6a′), 122.1 (CH, C-1′ or C-4′),

123.8 (quat, C-4a′ or C-10b′), 124.8 (CH, C-4′ or C-1′), 126.6 (quat, C-10b′ or C-4a′), 127.7 (CH, C-2′ or C-3′), 129.6 (CH, C-3′ or C-2′), 150.4 (quat, C-10a′), 152.8 (quat, C-5′), 170.7 (quat, amide), 174.8 (quat, C-8′); IR (film, NaCl) 1776 (lactone), 1743 (C=O), 1598 (C=C), 1392, 1331, 1168, 1138 cm^{-1}; *m/z* (LSIMS, %) 484 (M^++1, 63), 401 (21), 299 (19), 269 (100), 216 (31); HRMS analysis (LSIMS, M^++1) ($C_{25}H_{26}O_7NS$=484.1430); found *m/z* 484.1439.

Adduct **10** was also isolated as a colourless oil (16 mg, 33%): $[\alpha]_D$=−63.4 (*c*=0.7, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 3H, 8-Me_A), 1.34 (s, 3H, 8-Me_B), 1.25–2.38 (m, 7H, 6-CH, 7-CH_2, 4-CH_2 and 5-CH_2), 3.04–3.18 (m, 2H, 9′-CH_2), 3.45–3.61 (m, 2H, 3-H_A and 3-H_B), 4.24 (dd, *J*=7.7, 4.8 Hz, 1H, 6-H), 5.42–5.52 (m, 1H, 9a′-H), 6.50 (d, *J*=5.9 Hz, 1H, 6b′-H), 7.52–7.63 (m, 2H, 2′-H and 3′-H), 7.83–7.92 (m, 1H, 1′-H), 8.19–8.30 (m, 1H, 4′-H), 9.26 (bs, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8 (CH_3, 8-Me_A), 21.1 (CH_3, 8-Me_B), 26.5 (CH_2, C-5), 33.0 (CH_2, C-4), 34.3 (CH_2, C-9′), 37.9 (CH_2, C-7), 44.7 (CH, C-6), 47.9 (quat, C-18), 47.9 (quat, C-3a), 52.9 (CH_2, C-3), 65.5 (CH, C-7a), 82.5 (CH, C-9a′), 84.1 (CH, C-6b′), 103.5 (quat, C-6′), 107.2 (quat, C-6a′), 122.1 (CH, C-1′ or C-4′), 123.2 (quat, C-4a′ or C-10b′), 124.0 (CH, C-4′ or C-1′), 126.7 (quat, C-10b′ or C-4a′), 127.9 (CH, C-2′ or C-3′), 129.2 (CH, C-3′ or C-2′), 149.0 (quat, C-10a′), 153.0 (quat, C-5′), 171.2 (quat, amide), 173.8 (quat, C-8′); IR (film, NaCl) 3360 (OH), 1781 (lactone), 1678 (amide), 1598 (C=C), 1393, 1334, 1168, 1140 cm^{-1}; *m/z* (LSIMS, %) 484 (M^++1, 36), 401 (12), 268 (100), 223 (44); HRMS analysis (LSIMS, M^++1) ($C_{25}H_{26}O_7NS$=484.1430) found *m/z* 484.1447. For other Lewis acids see Table 3 in text.

*4.2.5. (−)-[3aS-(3aα,6α,7aβ)]-Hexahydro-8,8-dimethyl-1-[2′-carboxyethyl-5′-hydroxynaphtho[1,2-b]furan-4′-oyl]-3H-3a,6-methano-2,1-benzisothiazole-2,2-dioxide **14***

Both **9** and **10** proved to be highly unstable and opened to acid **14** (colourless oil) on standing: $[\alpha]_D$=−33.8 (*c*=1.3, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (quat, 3H, 8-Me_A), 1.36 (quat, 3H, 8-Me_B), 1.28–2.35 (m, 7H, 6-CH, 7-CH_2, 4-CH_2 and 5-CH_2), 3.40 (d, *J*=13.3 Hz, 1H, 3-H_A), 3.51 (d, *J*=13.3 Hz, 1H, 3-H_B), 3.95 (s, 2H, CH_2CO_2H), 4.19–4.33 (m, 1H, 7a-H), 6.92 (s, 1H, 3′-H), 7.44–7.72 (m, 2H, 7′-H and 8′-H), 8.16 (d, *J*=8.1 Hz, 1H, 9′-H), 8.38 (d, *J*=8.2 Hz, 1H, 6′-H) 12.00 (bs, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8 (CH_3, 8-Me_A), 21.1 (CH_3, 8-Me_B), 26.5 (CH_2, C-5), 33.0 (CH_2, C-4), 34.3 (CH_2, CH_2COOH), 37.9 (CH_2, C-7), 44.7 (CH, C-6), 47.9 (quat, C-8), 47.9 (quat, C-3a), 52.9 (CH_2, C-3), 65.5 (CH, C-7a), 103.7 (quat, C-2′), 110.9 (CH, C-3′), 119.8 (CH, C-6′ or C-9′), 121.2 (quat, C-5a′ or C-9a′), 122.1 (quat, C-9a′ or C-5a′), 124.9 (CH, C-9′ or C-6′), 125.1 (CH, C-7′ or C-8′), 131.4 (CH, C-8′ or C-7′), 149.1 (quat, C-9b′), 158.6 (quat, C-5′), 173.9 (quat, amide), 173.9 (quat, COOH); IR (film, NaCl) 3295 (OH), 1721 (acid), 1640 (amide), 1375, 1337, 1169, 1139 cm^{-1}; *m/z* (ESI, rel. abundance) 506 (M^++Na, 70), 484 (M^++1, 16), 269 (17); HRMS analysis (LSIMS, M^++1) ($C_{25}H_{26}O_7NS$=484.1430) found *m/z* 484.1438.

*4.2.6. (−)-(4R,6b′R,9a′R)- and (4R,6b′S,9a′S)-3-[5′-Hydroxy-8′-oxo-6b′,8′,9′,9a′-tetrahydrofuro[3,2-b]naphtho[2,1-d]furan-6′-oyl]-4-(phenylmethyl)-2-oxazolidinone **11** and **12***

Compounds **11** and **12** were prepared from quinone **4** (20 mg, 0.06 mmol) and TMS-furan (15 μL) using $ZnCl_2$ (1 equiv.) by the procedure described above.

Adduct **11** was isolated as a colourless oil (10 mg, 42%): $[\alpha]_D$=−25.8 (*c*=0.9, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 2.88 (dd, *J*=13.3, 10.2, 1H, CH_AH_BPh), 3.02–3.18 (m, 2H, 9′-CH_2), 3.61 (dd, *J*=13.3, 4.0 Hz, 1H, CH_AH_BPh), 4.17–4.40 (m, 2H, 5-H_A and 5-H_B), 4.92–5.17 (m, 1H, 4-H), 5.59 (ddd, *J*=6.4, 2.4, 6.4 Hz, 1H, 9a′-H), 6.26 (d, *J*=6.4 Hz, 1H, 6b′-H), 7.10–7.42 (m, 5H, Ph), 7.52–7.82 (m, 2H, 2′-H and 3′-H), 7.92 (d, *J*=7.5 Hz, 1H, 1′-H), 8.40 (d, *J*=7.6 Hz, 1H, 4′-H), 10.80 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.6 (CH_2, C-9′) 38.0 (CH_2, CH_2Ph), 55.9 (CH, C-4), 68.0 (CH_2, C-5), 80.7 (CH, C-9a′), 86.2 (CH, C-6b′), 103.6 (quat, C-6′), 122.2 (CH, C-1′ or C-4′), 124.4 (quat, C-4a′ or C-10b′),

124.8 (CH, C-4′ or C-1′), 127.0 (quat, C-10b′ or C-4a′), 127.3 (CH, Ph), 127.9 (CH, C-2′ or C-3′), 128.9 (CH, Ph), 130.2 (CH, C-3′ or C-2′), 134.9 (quat, Ph), 150.3 (quat, C-10a′), 153.7 (quat, C-2), 158.6 (quat, C-5′), 171.4 (quat, amide), 174.7 (quat, C-8′); IR (film) 1777 (s, amide), 1742 (lactone), 1680 (oxazolidinone), 1599 (C=C), 1391, 1353, 1155 cm^{-1}; *m/z* (CI, CH_4, rel. abundance) 446 (M^++1, 2), 355 (4), 206 (12), 178 (100), 85 (92); HRMS analysis (EI, M^+) ($C_{25}H_{19}O_7N$=445.1162) found *m/z* 445.1163.

Adduct **12** (6 mg, 24%) was isolated as a colourless oil (contaminated with 50% **11**): ^1H NMR (200 MHz, $CDCl_3$) δ (distinct minor diastereomer resonances only) 3.75 (dd, *J*=13.3, 4.0 Hz, 1H, CH_AH_BPh), 4.69–4.86 (m, 1H, 4-H), 6.03 (d, *J*=6.4 Hz, 1H, 6b′-H), 9.90 (s, 1H, OH); IR (film) 1783 (s, amide), 1691 (oxazolidinone), 1599 (C=C), 1396, 1339, 1149 cm^{-1}; *m/z* (EI, %) 445 (M^+, 5), 311 (38), 268 (100), 224 (57), 92 (67); HRMS analysis (EI, M^+) ($C_{25}H_{19}O_7N$=445.1162) found *m/z* 445.1176. For other Lewis acids see Table 4 in text.

4.3. (−)-(4R)-3-(2′-Carboxyethyl-5′-hydroxynaphtho[1,2-b]furan-4′-oyl)-4-(phenylmethyl)-2-oxazolidinone **15**

Both **11** and **12** proved to be highly unstable and opened to give acid **15** (yellow oil) on standing: $[\alpha]_D$=−28.2 (*c*=1.7, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 3.05 (dd, *J*=13.6, 9.2 Hz, 1H, CH_AH_BPh), 3.40 (dd, *J*=13.6, 2.7 Hz, 1H, CH_AH_BPh), 3.87 (s, 2H, CH_2CO_2H), 4.20–4.46 (m, 2H, 5-H_A and 5-H_B), 4.89–5.11 (m, 1H, 4-H), 6.34 (s, 1H, 3′-H), 7.07–7.38 (m, 5H, Ph), 7.44–7.72 (m, 2H, 7′-H and 8′-H), 8.12 (d, *J*=8.1 Hz, 1H, 9′-H), 8.42 (d, *J*=8.3 Hz, 1H, 6′-H), 11.47 (s, 1H, OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.1 (CH_2, CH_2CO_2H) 36.8 (CH_2, CH_2Ph), 53.4 (CH, C-4), 66.8 (CH_2, C-5), 103.6 (quat, C-2′), 107.1 (CH, C-3′), 119.8 (CH, C-6′ or C-9′), 120.8 (quat, C-5a′ or C-9a′), 122.6 (quat, C-9a′ or C-5a′), 125.0 (CH, C-9′ or C-6′), 125.1 (quat, C-7′ or C-8′), 127.4 (CH, Ph), 129.0 (CH, Ph), 129.4 (CH, Ph), 130.5 (CH, C-8′ or C-7′), 134.5 (quat, Ph), 149.5 (quat, C-9b′), 152.8 (quat, C-2), 159.0 (quat, C-5′), 172.5 (quat, amide), 173.8 (quat, COOH); IR (film) 1772 (s, amide), 1741, 1685 (oxazolidinone), 1386, 1346, 1210 cm^{-1}; *m/z* (CI, CH_4, rel. abundance) 355 (2), 206 (9), 178 (100), 85 (100); HRMS analysis (EI, M^+) ($C_{25}H_{20}O_7N$=446.1240) found *m/z* 446.1231.

4.3.1. (3′R)-Dihydro-4,4-dimethyl-2-oxo-3-furanyl (6bS,9aS)-5-methoxy-8-oxo-6b,8,9,9a-tetrahydrofuro[3,2-b]naphtho[2,1-d]furan-6-carboxylate **16**

A solution of naphthol **6** (200 mg, 0.5 mmol) in chloroform (50 mL) at 0°C was treated with silver(I) oxide (575 mg, 5 equiv.) and methyl iodide (150 μL, 2 equiv.). After stirring at room temperature overnight the mixture was filtered through Celite and the solvent removed *in vacuo*. The residue was purified by flash chromatography (hexane:ethyl acetate, 2:1) to give the title compound **16** as a colourless oil (48 mg, 23%): $[\alpha]_D$=−10.3 (*c*=0.8, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 3H, 4′-Me), 1.32 (s, 3H, 4′-Me), 3.06–3.20 (m, 2H, 9-CH_2), 4.03 (s, OMe), 4.04–4.23 (m, 2H, 5′-H_A and 5′-H_B), 5.48–5.58 (m, 1H, 9a-H), 5.73 (s, 1H, 3′-H), 6.58 (d, *J*=5.9 Hz, 1H, 6b-H), 7.58–7.70 (m, 2H, 2-H and 3-H), 7.92–8.02 (m, 1H, 1-H), 8.17–8.29 (m, 1H, 4-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2 (CH_3, 4′-Me), 23.1 (CH_3, 4′-Me), 35.5 (CH_2, C-9), 40.7 (quat, C-4′), 63.8 (CH_3, OMe), 75.9 (CH, C-3′), 76.7 (CH_2, C-5′), 82.1 (CH, C-9a), 85.3 (CH, C-6b), 114.8 (quat, C-6), 115.1 (quat, C-6a), 122.5 (CH, C-1 or C-4), 123.4 (quat, C-4a or C-10b), 124.3 (CH, C-4 or C-1), 126.7 (quat, C-10b or C-4a), 128.5 (CH, C-2 or C-3), 128.9 (CH, C-3 or C-2), 154.3 (quat, C-10a), 154.3 (quat, C-5), 162.9 (quat, ester), 172.8 (quat, C-2′), 174.6 (quat, C-8); IR (film) 1783 (lactone), 1737 (ester), 1672, 1595 (C=C), 1383, 1219, 1154 cm^{-1}; *m/z* (EI, %) 412 (M^+, 100), 367 (16), 283 ($C_{16}H_{11}O_5$, 49), 223 (30), 187 (36), 113 (28); HRMS analysis (EI, M^+) ($C_{22}H_{20}O_8$=412.1158) found *m/z* 412.1159.

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