

Addition of 2-[(trimethylsilyloxy)]furan to 2-acetyl-1,4-benzoquinone using chiral non-racemic copper(II)-pybox catalysts

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(received 05 Feb 03; accepted 07 Apr 03; published on the web 29 Apr 03)

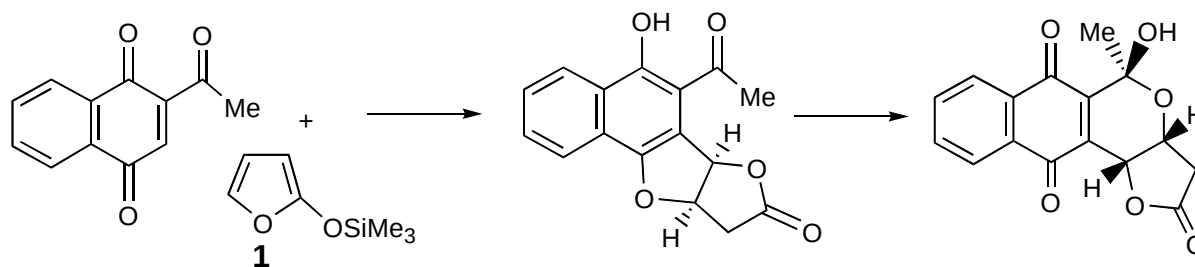
Abstract

The Michael addition of 2-[(trimethylsilyloxy)]furan **1** to 2-acetyl-1,4-benzoquinone **2** was carried out using several Cu(II)-pybox catalysts. The furobenzofuran adduct **3** was prepared in good chemical yield but in low enantiomeric excess. The adduct **3** was converted into the menthyl carbonate derivative to allow determination of the enantiomeric excess by high field NMR spectroscopy.

Keywords: 2-[(Trimethylsilyloxy)]furan, quinone, annulation, pybox ligands, pyranonaphthoquinones

Introduction

We have reported previously the uncatalyzed addition of 2-[(trimethylsilyloxy)]furan to 1,4-benzoquinones and 1,4-naphthoquinones that bear an electron withdrawing group at C-2, as an efficient entry into the furobenzofuran and furonaphthofuran annulation products, respectively.¹ The furonaphthofuran adducts then underwent smooth oxidative rearrangement to provide the pyranonaphthoquinone skeleton present in the isochromanquinone family of antibiotics (Scheme 1).² As part of an on-going programme directed towards designing an asymmetric variant of this annulation sequence we have also investigated³ the use of bis(oxazoline)-copper(II) complexes as enantiopure catalysts for the conjugate addition of 2-[(trimethylsilyloxy)]furan **1** to 2-acetyl-1,4-naphthoquinone. The aim was to prepare a chiral non-racemic furonaphthofuran intermediate, leading ultimately to enantioselective syntheses of several pyranonaphthoquinone antibiotics. This initial study proved disappointing in that only low enantioselection was observed, despite good literature precedent for high asymmetric induction using bidentate bis(oxazoline) (box) – copper(II) complexes in catalytic asymmetric Michael and Diels-Alder additions to substrates that can participate in catalyst chelation.⁴



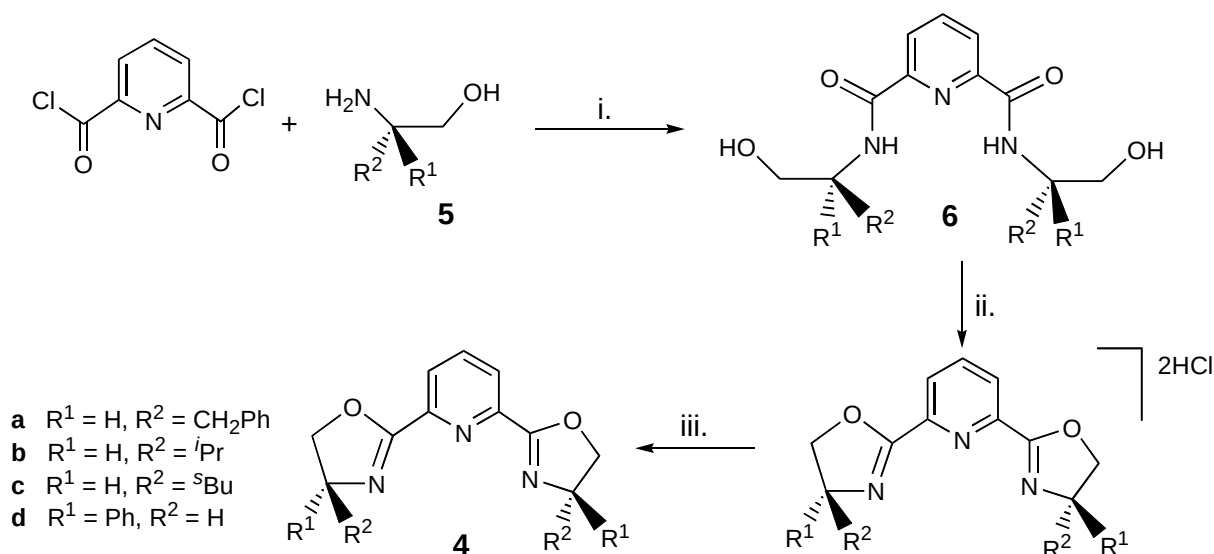
Scheme 1

Several recent papers^{5,6} have reported superior results using tridentate pyridine bis(oxazoline) (pybox) catalysts rather than bidentate phenyl bis(oxazoline) (box) catalysts for enantioselective Mukaiyama aldol reactions using silyl enol ethers. Moreover, copper(II)-pybox complexes have been shown to be efficient chiral catalysts for the enantioselective Mukaiyama-Michael reaction between (*E*)-3-crotonyl-1,3-oxazolidin-2-one and 2-[(trimethylsilyloxy)]furan.⁷ Therefore, we decided to evaluate the use of these pybox-metal complexes as catalysts for the enantioselective addition of 2-[(trimethylsilyloxy)]furan **1** to 2-acetyl-1,4-benzoquinone **2** (Table 1).

Discussion

Copper(II) complexes of four pybox ligands [(*S,S*)-(benzyl)-pybox] **4a**, [(*S,S*)-(iso-propyl)-pybox] **4b**, [(*S,S*)-(sec-butyl)-pybox] **4c**, and [(*R,R*)-(phenyl)-pybox] **4d** were synthesised and evaluated for their ability to catalyze the addition of 2-[(trimethylsilyloxy)]furan **1** to 2-acetyl-1,4-benzoquinone **2**. The pybox ligands were readily prepared by condensation of 2,6-pyridinedicarbonyl dichloride with either (*S*)-phenylalaninol **5a**, (*S*)-valinol **5b**, (*S*)-isoleucinol **5c** or (*R*)-phenylglycinol **5d** (Scheme 2). In turn, these latter amino alcohols were available from reduction of the appropriate amino acid with lithium borohydride-chlorotrimethylsilane.⁸

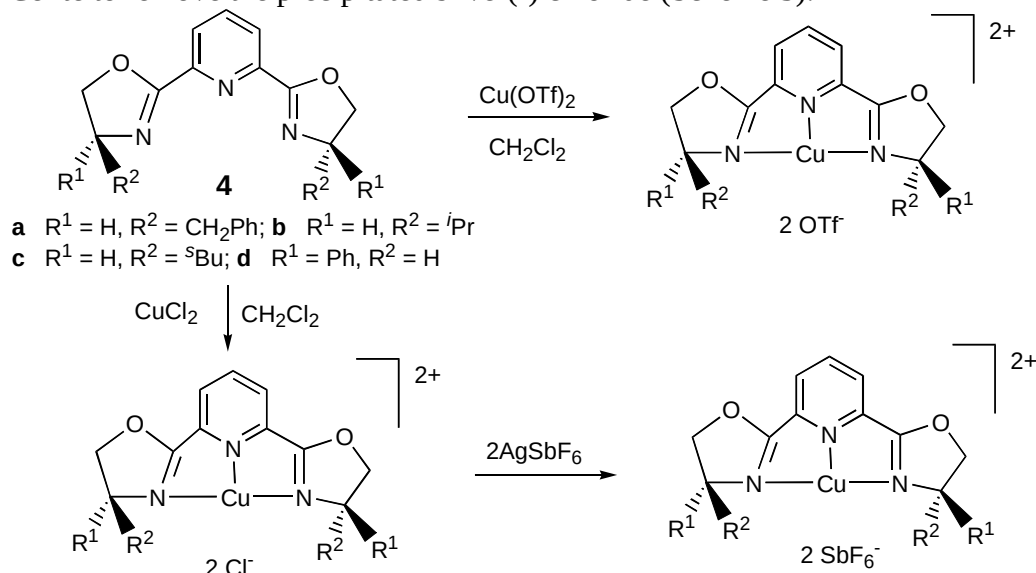
Two methods have been reported^{9,10} for the synthesis of pybox ligands. In our hands, we found that a combination of these two approaches allowed a successful synthesis of the desired ligands **4a-d**. The appropriate amino alcohol **5** dissolved in isopropyl acetate was added to a solution of 1.5 mol L⁻¹ aqueous potassium hydrogencarbonate. A solution of pyridine-2,6-dicarbonyl dichloride in chloroform was added and the mixture was heated at reflux for 2.5 h, affording the bisamide **6** in high yield. The open pybox bisamide **6** was then dissolved in chloroform and treated with thionyl chloride to promote ring closure to the pybox ligand **4**, initially as its bis(hydrochloride) salt. This salt was surprisingly resistant towards neutralization, requiring treatment with 3 mol L⁻¹ aqueous sodium hydroxide in methanol for 3 days to liberate the pybox ligand **4** as the free base.



Reagents and Conditions: i. $i\text{PrOAc}$, $1.5 \text{ mol L}^{-1} \text{ KHCO}_3$; ii. SOCl_2 , heat, CHCl_3 ; iii. $3 \text{ mol L}^{-1} \text{ NaOH}$, MeOH , room temp., 3 days.

Scheme 2

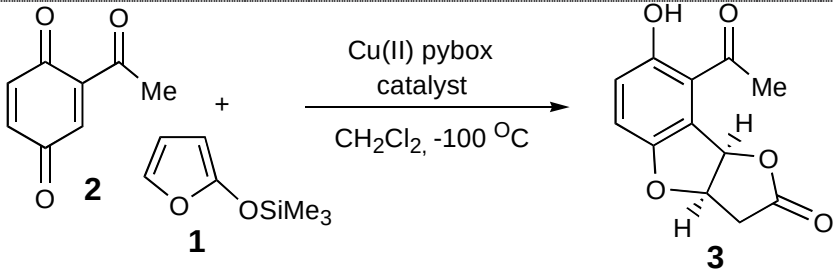
Given that higher levels of asymmetric induction were observed¹¹ in Diels-Alder reactions catalyzed by box-copper(II) complexes when the non-coordinating hexafluoroantimonate counterion was used, both pybox-copper(II) triflate and hexafluoroantimonate complexes were evaluated in the present study. The chiral pybox-copper(II) triflate complexes were formed by reacting pybox ligands **4a-d** with copper(II) triflate in dichloromethane at room temperature for 4 h in the presence of 4 Å molecular sieves, giving characteristically blue solutions (Scheme 3). The cationic hexafluoroantimonate complexes were prepared by anion exchange from the pre-formed copper(II) chloride complex using silver(I) hexafluoroantimonate, followed by filtration through Celite to remove the precipitated silver(I) chloride (Scheme 3).



Scheme 3

Initial work (Table 1) focussed on the use of the catalyst prepared from the benzyl pybox ligand **4a** and copper(II) triflate to induce asymmetry in the addition of 2-[(trimethylsilyloxy)]furan **1** to 2-acetyl-1,4-benzoquinone **2**. Disappointingly, use of 5-37 mol% catalyst afforded only the adduct **3** as a racemate. Use of a stoichiometric quantity (1 equiv.) of the copper(II) triflate complex also afforded near-racemic adduct **3**, prompting investigation of hexafluoroantimonate as an alternative counterion. Although the use of this latter complex in stoichiometric amount increased the chemical yield of adduct **3**, again it was racemic.

Table 1. Reaction of 2-[(trimethylsilyloxy)]furan **1** with 2-acetyl-1,4-benzoquinone **2** using pyridine bis(oxazoline)-copper complexes

				
Ligand	Counterion	mol% Catalyst	Yield 3 (%)	e.e. (%) ^a
4a	OTf ⁻	5	25	0
4a	OTf ⁻	37	53	0
4a	OTf ⁻	100	54	9
4a	SbF ₆ ⁻	100	76	0
4b	OTf ⁻	5	21	0
4b	OTf ⁻	37	46	0
4b	OTf ⁻	100	63	33 ^b
4b	SbF ₆ ⁻	37	60	0
4b	SbF ₆ ⁻	100	18	0
4c	OTf ⁻	100	72	0
4d	OTf ⁻	5	43	0
4d	OTf ⁻	37	58	0
4d	OTf ⁻	100	59	0
4d	SbF ₆ ⁻	100	94	0

^a % e.e. of **3** measured by integration of the ¹H NMR spectrum obtained for the diastereomeric menthyl carbonate derivatives formed upon reaction with (+)-menthyl chloroformate.

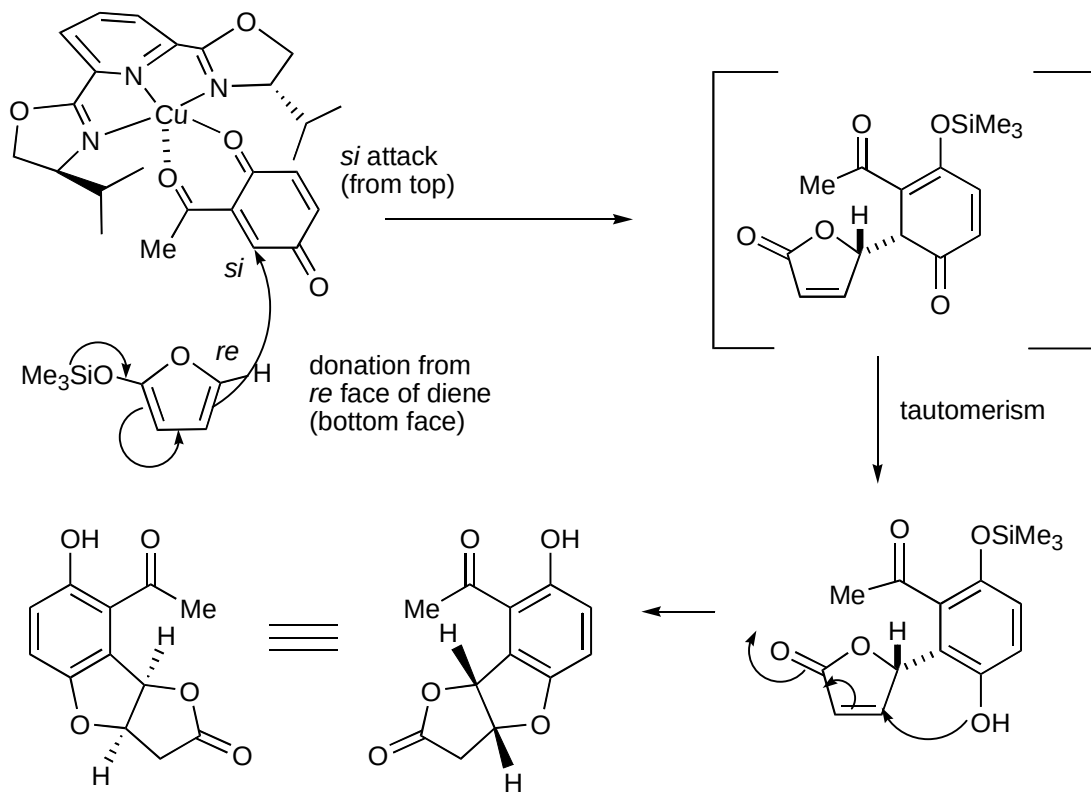
^b Absolute configuration of major enantiomer not determined.

These results were mirrored in those obtained for the copper(II) complexes of the analogous phenyl pybox ligand **4d**; no enantioselection was observed despite using up to a stoichiometric

quantity of either the triflate or hexafluoroantimonate complex. The only evidence for stereoselection observed in the reaction of 2-[(trimethylsilyloxy)]furan **1** with 2-acetyl-1,4-benzoquinone **2** arose from the use of a stoichiometric quantity of the copper(II) triflate complex of the pybox ligand **4b** derived from valinol, which afforded the enantiomers of adduct **3** in a ratio of 2:1. However, use of the analogous sec-butyl pybox ligand **4c** under the same conditions reverted to the formation of adduct **3** as a racemate.

The enantioselectivity of the reaction was determined by conversion of the adduct **3** into its diastereoisomeric menthyl carbonate derivatives by reaction with (+)-menthyl chloroformate. Integration of the doublets observed at δ 0.81 ppm and δ 0.83 ppm for the menthyl CHCH_3 groups at C5' of the individual diastereoisomers allowed determination of their ratio.

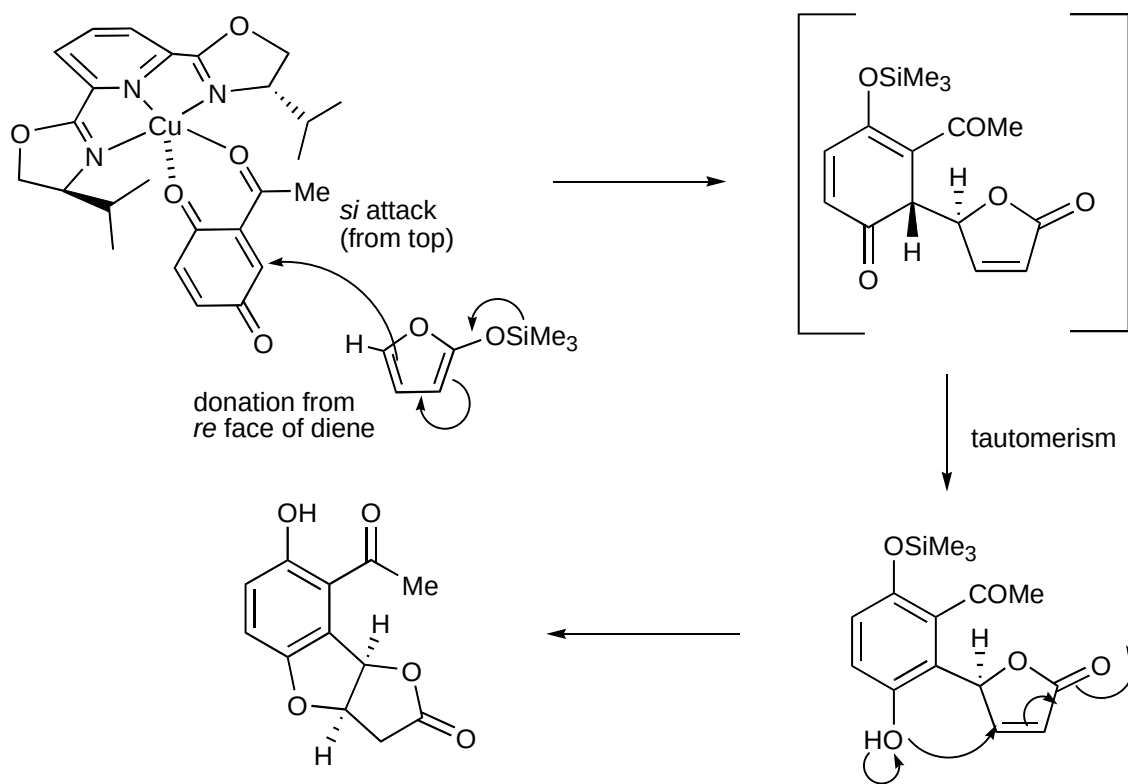
It has been established that 2-[(trimethylsilyloxy)]furan **1** adds as a nucleophile in a Michael type fashion to C3 of the benzoquinone **2**.¹² There is an opportunity for asymmetric catalysis if the two adjacent carbonyl oxygens of the benzoquinone preferentially form a bidentate chelate to the Lewis acid metal centre from one face. The structure of $\{\text{Cu}[(S,S)\text{-(isopropyl)-pybox}]\}(\text{SbF}_6)_2$ containing a bound substrate (via bidentate chelation) has been determined by EPR spectroscopy, and this evidence supported the hypothesis that substrates bind to this catalyst in a five-coordinate square pyramidal geometry.¹³ In the Michael addition pathway, it is thought that the two electronegative triflate counterions are displaced successively by the two adjacent carbonyl oxygens on the 2-acetylbenzoquinone, resulting in square pyramidal geometry of the catalyst-substrate complex.



Scheme 4

In the enantioselective annulation in the presence of a stoichiometric amount of $[\text{Cu}((S,S)\text{-valinol-pybox})](\text{OTf})_2$ to give furofuran **3**, it appears that the adjacent carbonyl oxygens have formed a bidentate chelate to Cu(II) from one face selectively, resulting in the observed ratio of 2:1. Under all of the reaction conditions which resulted in racemic **3**, the two adjacent carbonyl oxygens presumably also formed a bidentate chelate to the Lewis acid metal centre, but conjugate addition then occurred equally from both the *re* face and the *si* face. Scheme 4 shows *si* face attack on the chelated enone, and donation of electrons from the *re* face of the diene. This *si*, *re* approach would lead to (*R,R*)-stereochemistry in the *syn* furobenzofuran adduct **3**. The alternative *re*, *si* approach would lead to the (*S,S*)-stereochemistry.

Because of the C_2 symmetry of the ligand, there is an alternative bidentate coordination which places the acetyl oxygen in the square plane (Scheme 5). Again, there are two trajectories of approach possible; Scheme 5 shows *si*,*re* interaction leading to (*R,R*); and *re*,*si* would again afford (*S,S*). It is assumed that the approach trajectory which minimises steric interaction with an isopropyl group is favoured, leading to 33% ee at best.

**Scheme 5**

In summary the work reported herein focuses on the use of bis(oxazoline)pyridine-copper(II) complexes as chiral catalysts for development of an asymmetric addition of 2-[(trimethylsilyloxy)]furan to 2-acetyl-1,4-benzoquinone. The results obtained indicate that even when a stoichiometric quantity of the metal complex is used only a moderate level of enantioselectivity is observed.

Experimental Section

General Procedures. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. Infrared spectra were recorded with a Perkin-Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. ^1H and ^{13}C NMR spectra were recorded as indicated on either a Bruker AC200 spectrometer operating at 200 MHz for ^1H nuclei and 50 MHz for ^{13}C nuclei, a Bruker DRX300 spectrometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei, or a Bruker DRX400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei. Both ^1H and ^{13}C NMR spectra were interpreted with the aid of COSY, HETCOR and DEPT 135 experiments and are reported in p.p.m. downfield from tetramethylsilane as reference. High-resolution mass spectra were recorded using a VG 7070 spectrometer operating with an ionisation potential of 70 eV at a nominal resolution of 5000 or 10000 as appropriate. Fast atom bombardment (FAB+) spectra were recorded from *m*-nitrobenzyl alcohol as matrix. Major fragments are assigned where possible and their intensities given as percentages of the base peak. Tetrahydrofuran was dried using sodium/benzophenone and distilled prior to use. Flash chromatography was performed using either Merck Kieselgel 60 or Riedel-de-Haën Kieselgel S silica gel (both 230-400 mesh), or Merck aluminum oxide (70-230 mesh), with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine vapour or with vanillin in methanolic sulfuric acid.

2-Acetyl-1,4-benzoquinone (2). A mixture of 2,5-dihydroxyacetophenone (0.77 g, 5.0 mmol) and anhydrous sodium sulfate (1.5 g) in dry toluene (10 mL) was stirred with silver(I) oxide (2.3 g, 10.0 mmol) for 2.5 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 **2** (0.61 g, 80%) as dark orange crystals; m.p. 60-65 °C (lit.¹⁴ m.p. 64-65.5 °C).

(R)-2-Amino-2-phenylethanol (5d) (D-phenylglycinol). LiBH₄ (0.88 g) was dissolved in THF (30 mL), and chlorotrimethylsilane (10 mL, 8.624 g, 80 mmol) was added slowly followed by D-phenylglycine (3.1 g, 20 mmol) in one portion. The white reaction mixture was stirred at room temperature for 20.5 h. The reaction was quenched by slow addition of MeOH (*ca* 20 mL) until there was no more effervescence and the solution was orange. After cooling the mixture to room temperature the solvents were removed on a rotary evaporator leaving an orange oily residue. The sticky orange solid residue was dissolved in aqueous NaOH (50 mL, 3.6 mol L⁻¹) and extracted with dichloromethane (3 x 50 mL). The yellow organic phase was dried (Na₂SO₄) and concentrated under reduced pressure to afford a yellow solid (2.6 g, 92%) that was recrystallized

from ethyl acetate to afford (*R*)-2-amino-2-phenylethanol **5d** (2.17 g, 78%) as colourless needles; m.p. 72-75 °C (lit.¹⁵ m.p. 69-71 °C); $[\alpha]_D^{20} = -30.4^\circ$ ($c = 0.69$, 1 mol L⁻¹ HCl) (lit.¹⁵ $[\alpha]_D^{24} = -32^\circ$ ($c = 0.75$, 1 mol L⁻¹ HCl)).

(S)-2-Amino-3-phenylpropanol (L-Phenylalaninol) (5a). Using a procedure similar to that described above for (*R*)-2-amino-2-phenylethanol **5d**, (*S*)-2-amino-3-phenylpropanol **5a** was prepared from (L)-phenylalanine, lithium borohydride and chlorotrimethylsilane in 87% yield as a colourless solid; m.p. 92-94 °C; lit. m.p.¹⁵ 90-92 °C; $[\alpha]_D^{20} = -22.7^\circ$ ($c = 1.2$, 1 mol L⁻¹ HCl) (lit.¹⁵ $[\alpha]_D^{24} = -22^\circ$ ($c = 1.2$, 1 mol L⁻¹ HCl)).

(S)-2-Amino-3-methylpentanol (L-Valinol) (5b). Using a procedure similar to that described above for (*R*)-2-amino-2-phenylethanol **5d**, (*S*)-2-amino-3-methylbutanol **5b** was prepared from (L)-valine, lithium borohydride and chlorotrimethylsilane in 87% yield as a colourless thick viscous oil; $[\alpha]_D^{20} = +16.7^\circ$ ($c = 10.0$, EtOH) (lit.¹⁵ $[\alpha]_D^{24} = +17^\circ$ ($c = 10.0$, EtOH)).

(S)-3-Methyl-2-aminopentanol (L-Isoleucinol) (5c). Using a procedure similar to that described above for (*R*)-2-amino-2-phenylethanol **5d**, (*S*)-3-methyl-2-aminopentanol **5c** was prepared from (L)-isoleucine, lithium borohydride and chlorotrimethylsilane in 84% yield as a colourless oil; b.p. 115 °C/15 mmHg; lit. b.p.¹⁵ 100-101 °C/5 mmHg; $[\alpha]_D^{20} = +3.8^\circ$ ($c = 0.98$, EtOH) (lit.¹⁵ $[\alpha]_D^{24} = +3.5^\circ$ ($c = 1.0$, EtOH)).

Pyridine-2,6-dicarbonyl dichloride.^{16,17} Pyridine-2,6-dicarboxylic acid (3.05 g, 17.9 mmol) was dissolved in thionyl chloride (20 mL) and the mixture heated at reflux for 8 h using a Liebig condenser fitted with a CaCl₂ drying tube. After leaving the mixture to stand overnight, the excess thionyl chloride was removed by distillation. The residue was placed under high vacuum for several hours to afford pyridine-2,6-dicarbonyl dichloride (3.63 g, 99%) as pale cream crystals; m.p. 132-137 °C; (Found: M⁺, 202.9537, C₇H₃³⁵Cl₂NO₂ requires 202.9541; 204.9508, C₇H₃³⁵Cl³⁷ClNO₂ requires 204.9511; 206.9481, C₇H₃³⁷Cl₂NO₂ requires 206.9482); $\nu_{\max}$ (film)/cm⁻¹ 1755 (C=O), 876 (C-Cl); δ_H (200 MHz, CDCl₃) 8.23 (1H, t, *J* 7.3 Hz, H4), 8.43 (2H, d, *J* 7.4 Hz, H3, H5); δ_C (50 MHz, CDCl₃) 129.0 (C-3, C-5), 139.4 (C-4). *m/z* 207 (M⁺, 10%), 205 (M⁺, 56%), 203 (MH⁺, 86%), 170 (207-³⁷Cl, 33%), 168 (203-³⁵Cl, 100%), 142 (170-CO, 34%), 140 (168-CO, 34%), 114 (142-CO, 7%), 112 (140-CO, 21%), 76(C₅H₅N⁺), 63 (CO³⁵Cl, 10%).

***N,N'*-Bis[(*R*)-2-hydroxy-1-phenylethyl]pyridine-2,6-dicarboxamide (6d).** (*R*)-2-Amino-2-phenylethanol **5d** (D-phenylglycinol) (1.0 g, 7.30 mmol) was added to a solution of potassium hydrogencarbonate (0.78 g, 7.82 mmol) in H₂O (5.2 mL). Isopropyl acetate (10 mL) and ethyl acetate (14 mL) were mixed together and added. The resulting colourless mixture was heated to 60-70 °C. Pyridine-2,6-dicarbonyl dichloride (0.75 g, 3.68 mmol) was dissolved in chloroform (4.5 mL) and this solution was added dropwise *via* syringe over 5 min. The mixture was heated under reflux for 2.5 h, then left to cool with stirring overnight. The aqueous phase was extracted with ethyl acetate (2 x 35 mL), and the combined organic phases were dried (Na₂SO₄) and evaporated under reduced pressure to give the title bisamide **6d** (1.45 g, 98%) as a colourless foamy solid; m.p. 72-75 °C; $[\alpha]_D^{20} = -30.4^\circ$ ($c = 0.69$, 1 M HCl); (Found: MH⁺, 406.1770, C₂₃H₂₄N₃O₄ requires 406.1769); $\nu_{\max}$ (film)/cm⁻¹ 3435 (OH), 1692 (amide CONH); δ_H (200 MHz, CDCl₃) 2.17 (1H, s, OH), 3.42 (2H, bs, H-1'), 5.25 (1H, apparent doublet, H-2'), 7.2-7.4

(10H, m, Ph), 7.85 (1H, t, J 7.7, H-4), 8.18 (1H, d, J 7.7, H-4), 8.87 (1H, d, J 7.5, NH); δ_{C} (50 MHz, CDCl_3) 55.8 (CH, CHN), 65.9 (CH_2 , CH_2OH), 125.1 (CH, C-3), 126.7 (CH, C-2'), 127.8 (CH, C-4'), 128.8 (CH, C-3'), 138.8 (C, Ph), 139.0 (CH, C-4), 148.5 (C, C-2), 163.8 (C, C=O); m/z 406 (MH^+ , 4%), 388 ($\text{MH}^+ - \text{H}_2\text{O}$, 3.4%), 372 (388-O, 18%), 370 ($\text{MH}^+ - 2\text{H}_2\text{O}$, 27%), 268 ($\text{MH}^+ - \text{C}_8\text{H}_{10}\text{ON}$, 34%), 250 (268- H_2O , 17%), 120 ($\text{C}_8\text{H}_9\text{O}$, 100%) 106 ($\text{C}_6\text{H}_9\text{ON}$).

2,6-Bis[(4R)-4,5-dihydro-4-phenyl-2-oxazolyl]pyridine (4d).^{9,10} Thionyl chloride (2.4 mL, 3.9 g, 33.05 mmol) was added with stirring to a solution of *N,N'*-bis[(R)-2-hydroxy-1-phenylethyl]pyridine-2,6-dicarboxamide **6d** (1.34 g, 3.30 mmol) in chloroform (20 mL). The mixture was heated under reflux for 3 h, then cooled in ice. Water was added through the top of the condenser to quench the excess thionyl chloride and the aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organic phases were washed with saturated aqueous NaHCO_3 (10-15 mL) and brine (10-15 mL), and then dried (Na_2SO_4). The solvent was removed at reduced pressure to give 2,6-bis[(4R)-4,5-dihydro-4-phenyl-2-oxazolyl]pyridine dihydrochloride as a pale brown solid (1.43 g, 97%); ν_{max} (film)/ cm^{-1} 3325 (NH), 1656 (C=N), 1527 (C=C).

The bis(hydrochloride) salt (1.43 g, 3.2 mmol) was dissolved in MeOH (approx. 25 mL) and treated with aqueous NaOH (8.4 mL, 3 mol L^{-1}), affording a cloudy orange-light brown solution. The mixture was stirred at room temperature under a nitrogen atmosphere for 73 h, and then extracted with dichloromethane (2 x 50 mL). The organic phase was dried (Na_2SO_4) and the solvents removed under reduced pressure to afford a creamy-yellow solid that was dissolved in hot (near boiling) ethyl acetate, assisted with a small quantity of MeOH. Hexane was added, and the flask was left to cool to room temperature then placed in a refrigerator for at least 1 h. The resultant colourless crystals were filtered off, and washed with cold ethyl acetate and cold hexanes to give 2,6-bis[(4R)-4,5-dihydro-4-phenyl-2-oxazolyl]pyridine **4d** (1.04 g, 89%), m.p. 168-70 °C; lit.¹⁰ m.p. 170-172 °C; $[\alpha]_{\text{D}}^{20} = +180.3^\circ$ ($c = 1.0$, CH_2Cl_2); lit.¹⁰ $[\alpha]_{\text{D}}^{20} = +183.5^\circ$ ($c = 1.03$, CH_2Cl_2); (Found: MH^+ 370.1551, $\text{C}_{23}\text{H}_{20}\text{N}_3\text{O}_2$ requires 370.1556); ν_{max} (film)/ cm^{-1} 1651 (C=N), 1568 (C=C); δ_{H} (200 MHz) 4.41 and 4.45 (2H, dd, J 8.5 and 9.5 Hz, H-5'B), 4.91 and 4.96 (2H, dd, J 10.4 and 10.1, H-5'A), 5.46 (1H, apparent t, J 9.5, H-4'), 7.26-7.41 (10H, m, Ph), 7.93 (1H, t, J 7.8 Hz, H-4), 8.34 (1H, d, J 7.8, H3 and H5); δ_{C} (50 MHz) 70.3 (CH, C-4'), 75.5 (CH_2 , C-5'), 126.3 (CH, C-3), 126.8 (CH, C-2''), 127.8 (CH, C-4''), 128.8 (CH, C-3''), 137.5 (CH, C-4), 141.6 (C, Ph), 146.6 (C, C-2), 163.4 (C, C-2'); m/z 761 ($2\text{M} + \text{Na}^+$), 739 ($2\text{M} + \text{H}$), 392 ($\text{M} + \text{Na}^+$), 370 (MH^+ , 100%), 250 ($\text{M} - \text{C}_8\text{H}_8\text{O}$), 223 ($\text{M} - \text{C}_9\text{H}_9\text{ON}$, 7%).

***N,N'*-bis[(S)-(2-hydroxy-1-(phenylmethyl)ethyl)]pyridine-2,6-dicarboxamide (6a).** Using a procedure similar to that described above for bisamide **6d**, bisamide **6a** was prepared from pyridine-2,6-dicarbonyl chloride (0.66 g, 3.2 mmol) and (L)-phenylalaninol **5a** (1.0 g, 6.6 mmol) in 94% yield as a colourless solid; m.p. 98-100 °C; (Found: M^+ , 433.1997, $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_4$, requires 433.2002); ν_{max} (film)/ cm^{-1} 3323 (OH, NH), 1649 (amide CONH); δ_{H} (200 MHz, CDCl_3) 2.35 (2H, bs, OH), 3.02 (4H, d, J 7.1, CH_2Ph), 3.71-3.87 (4H, m, CH_2O), 4.32-4.42 (2H, m, CHN), 7.19-7.36 (10H, m, Ph), 7.95-8.02 (3H, m, H-4 and NH), 8.29 (2H, d, J 7.9, H-3); δ_{C} (50 MHz, CDCl_3) 37.0 (CH_2 , CH_2Ph), 53.0 (CH, CHN), 63.8 (CH_2 , CH_2O), 125.1 (CH, C-3), 126.8 (CH, Ph), 128.7 (CH, Ph), 129.3 (CH, Ph), 137.5 (C, Ph), 139.1 (CH, C-4), 148.5 (C, C-2), 163.7 (C,

C=O); m/z 433 (M^+ , 2 %), 342 (M-C₇H₇, 100), 324 (342-H₂O, 40), 306 (324-H₂O, 12), 237 (306-C₅H₉, 8).

2,6-Bis[(4S)-4,5-dihydro-4-(phenylmethyl)-2-oxazolyl]pyridine (4a).^{18,19} Using a procedure similar to that described above for the preparation of phenyl pybox **4d** from bisamide **6d**, bisamide **6a** was treated with thionyl chloride to afford 2,6-bis[(4S)-4,5-dihydro-4-(phenylmethyl)-2-oxazolyl]pyridine hydrochloride (1.76 g, 78%) as a colourless solid; m.p. 135-136 °C; $\nu_{\max}$ (film)/cm⁻¹ 3310 (NH), 1673 (C=N); δ_H (400 MHz, CDCl₃) 3.06-3.16 (4H, m, CH₂Ph), 3.70 (2H, dd, J 2.9, and J 11.3, H-5'A), 3.81 (2H, dd, J 3.9, and J 11.3, H-5'B), 4.68-4.74 (2H, m, H-4'), 7.27-7.38 (10H, m, Ph), 8.05-8.11 (3H, m, H-4 and NH), 8.37 (2H, d, J 7.8, H-3); δ_C (50 MHz, CDCl₃) 37.6 (CH₂, CH₂Ph), 46.8 (CH₂, C-5'), 50.8 (CH, C-4'), 125.1 (CH, C-3), 127.1 (CH, Ph), 128.8 (CH, Ph), 129.3 (CH, Ph), 136.7 (CH, C-4), 139.2 (C, Ph), 148.4 (C, C-2), 162.7 (C, C-2'); m/z (FAB+), 470 (MH^+ , 50 %), 434 (M-HCl, 2), 378 (M-C₆H₆N, 10), 168 (226-C₃H₈N, 13). The bis(hydrochloride) salt was then treated with NaOH in MeOH for 3 days (as described above for phenyl pybox **4d**) to give 2,6-bis[(4S)-4,5-dihydro-4-(phenylmethyl)-2-oxazolyl]pyridine **4a** (0.91 g, 71%) as colourless crystals, m.p. 155-157 °C; lit.¹⁸ m.p. 156 °C; $[\alpha]_D^{25} = -37.3^\circ$ ($c = 0.66$, CHCl₃); lit.¹⁹ $[\alpha]_D^{25} = -38^\circ$ ($c = 0.67$, CHCl₃); (Found: M^+ , 397.1792, C₂₅H₂₃N₃O₂, requires 397.1790); δ_H (200 MHz, CDCl₃) 2.74 (2H, dd, J 8.8 and J 13.7, CH_AH_BPh), 3.26 (2H, dd, J 5.1 and J 13.7, CH_AH_BPh), 4.25 (2H, dd, J 7.8 and J 8.6, H-5'A), 4.45 (2H, t, J 8.3, H-5'B), 4.60-4.73 (2H, m, H-4'), 7.17-7.35 (10H, m, Ph), 7.87 (1H, dd, J 7.5 and J 8.2, H-4), 8.21 (2H, d, J 7.8, H-3); δ_C (50 MHz, CDCl₃) 41.5 (CH₂, CH₂Ph), 68.0 (CH, C-4'), 72.4 (CH₂, C-5'), 125.7 (CH, C-3), 126.5 (CH, Ph), 128.5 (CH, Ph), 129.1 (CH, Ph), 137.2 (CH, C-4), 137.6 (C, Ph), 146.7 (C, C-2), 162.6 (C, C-2'); m/z 397 (M^+ , 10 %), 306 (M-C₇H₇, 100), 278 (306-CO, 11), 214 (306-C₆H₆N, 8). The ¹H and ¹³C NMR data were in agreement with the literature values.¹⁸

N,N'-bis[(S)-(1-hydroxymethyl-2-methylpropyl)]pyridine-2,6-dicarboxamide (6b).²⁰ Using a procedure similar to that described above for bisamide **6d**, bisamide **6b** was prepared from pyridine-2,6-dicarbonyl dichloride (3.4 g, 16.7 mmol) and (L)-valinol **5b** (3.45 g, 33.4 mmol) in 97% yield as a colourless solid, m.p. 83-85 °C; (Found: M^+ , 337.2002, C₁₇H₂₇N₃O₄, requires 337.2002); $\nu_{\max}$ (film)/cm⁻¹ 3311 (OH and NH), 1647 (amide CONH); δ_H (200 MHz, CDCl₃) 1.03 (6H, d, J 4.4, CH₃), 1.06 (6H, d, J 4.4, CH₃), 2.03-2.25 [4H, m, OH and CH(CH₃)₂], 3.84 (4H, d, J 4.6, CH₂OH), 3.90-4.00 (2H, m, H-1'), 8.01-8.08 (3H, m, H-4 and NH), 8.34 (2H, d, J 7.8, H-3); δ_C (50 MHz, CDCl₃) 18.6 (CH₃), 19.7 (CH₃), 29.3 [CH, CH(CH₃)₂], 57.2 (CH, CHN), 63.9 (CH₂, CH₂O), 125.1 (CH, C-3), 139.3 (CH, C-4), 148.7 (C, C-2), 164.1 (C=O); m/z 337 (M^+ , 2 %), 322 (M-CH₃, 3 %), 306 (M-CH₂OH, 100), 294 (M-C₃H₇, 29), 288 (306-H₂O, 25), 220 (288-C₄H₆N, 15).

2,6-Bis[(4S)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]pyridine (4b). Using a procedure similar to that described above for the preparation of phenyl pybox **4d** from bisamide **6d**, bisamide **6b** (5.47 g, 1.6 mmol) was treated with thionyl chloride to afford 2,6-bis[(4S)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]pyridine hydrochloride (4.38 g, 70%) as a cream solid. The bis(hydrochloride) salt was treated immediately with NaOH in MeOH for 3 days (as described above for phenyl pybox **4d**) to give 2,6-bis[(4S)-4,5-dihydro-4-(1-methylethyl)-2-

oxazolyl]pyridine **4b** (3.24 g, 64%) as colourless needles, m.p. 151-153 °C; lit.²⁰ m.p. 151-154°; $[\alpha]_D^{25} = -117.4^\circ$ (c = 0.7, CH₂Cl₂); lit.¹⁰ $[\alpha]_D^{25} = -116.8^\circ$ (c = 1.0, CH₂Cl₂); (Found: M⁺ 301.1787, C₁₇H₂₃N₃O₂, requires 301.1790); $\nu_{\max}$ (film)/cm⁻¹ 1636 (C=N); δ_H (200 MHz, CDCl₃) 0.94 (6H, d, *J* 6.7, CH₃), 1.05 (6H, d, *J* 6.7, CH₃), 1.83-1.93 (2H, m, CHCH₃), 4.08-4.27 (4H, m, H-5'A and H-4'), 4.54 (2H, dd, *J* 7.8 and *J* 8.8, H-5'B), 7.86 (1H, t, *J* 7.8, H-4), 8.21 (2H, d, *J* 7.8, H-3); δ_C (50 MHz, CDCl₃) 18.3 (CH₃), 19.0 (CH₃), 32.8 (CH, CHCH₃), 71.0 (CH, C-4'), 73.0 (CH₂, C-5'), 125.7 (CH, C-3), 137.2 (CH, C-4), 146.9 (C, C-2), 162.2 (C, C-2'); *m/z* 301 (M⁺, 3 %), 286 (M-CH₃, 2 %) 258 (M-C₃H₇, 100), 230 (M-C₃H₇CO, 22).

***N,N'*-bis[(*S*)-(1-hydroxymethyl-2-methylbutyl)]pyridine-2,6-dicarboxamide (6c).** Using a procedure similar to that described above for bisamide **6d**, bisamide **6c** was prepared from pyridine-2,6-dicarbonyl chloride (0.87 g, 4.9 mmol) and (L)-isoleucinol **5c** (1.03 g, 8.5 mmol) in 91% yield as a foamy solid; m.p. 90-95 °C; $[\alpha]_D^{20} = -77.2^\circ$ (c = 0.94, EtOH); (Found: MH⁺ 366.23928, C₁₉H₃₂N₃O₄ requires 366.23928); $\nu_{\max}$ (film)/cm⁻¹ 3721 (OH and NH), 1690 (amide CONH); δ_H (200 MHz, CDCl₃) 0.94-0.98 (12H, m, CH₂CH₃, CHCH₃), 1.40-1.80 (6H, m, CHMe, CH₂Me), 3.78 (4H, m, CH₂OH), 4.24 (2H, m, CHN), 8.0 (1H, t, *J* 7.8 Hz, H4), 8.1 (2H, d, *J* 7.7 Hz, NH), 8.29 (2H, d, *J* 7.7 Hz, H3, H5); δ_C (200 MHz, CDCl₃) 22.3 (CH₃), 23.0 (CH₃), 25.0 (CH, C₄H₉), 40.1 (CH₂, CH₂CH₃), 50.1 (CH, CHN), 65.5 (CH₂, CH₂OH), 125.0 (CH, C-3), 139.0 (CH, C-4), 149.1 (C, C-2), 163.3 (C=O); *m/z* 366 (MH⁺, 100%), 334 (M⁺-CH₂OH, 15%).

2,6-Bis[(4*S*)-4,5-dihydro-4-(2-methylpropyl)-2-oxazolyl]pyridine (4c). Using a procedure similar to that described above for the preparation of phenyl pybox **4d** from bisamide **6d**, bisamide **6c** was treated with thionyl chloride to afford 2,6-bis[(4*S*)-4,5-dihydro-4-(2-methylpropyl)-2-oxazolyl]pyridine hydrochloride as a cream solid; $\nu_{\max}$ (film)/cm⁻¹ 3495 (NH), 1660 (C=N); (Found: MH⁺ 402.1708, C₁₉H₃₀³⁵Cl₂N₂O₃ requires 402.1715; MH⁺ 404.1682, C₁₉H₃₀³⁵Cl³⁷Cl N₂O₃ requires 404.1686; MH⁺ 406.1672, C₁₉H₃₀³⁷Cl₂N₂O₃ requires 406.1656). The bis(hydrochloride) salt was then treated with NaOH in MeOH for 3 days (as described above for phenyl pybox **4d**) to give 2,6-bis[(4*S*)-4,5-dihydro-4-(2-methylpropyl)-2-oxazolyl]pyridine **4c** in 44% overall yield, m.p. 115-118 °C; $[\alpha]_D^{20} = -144.1^\circ$ (c = 0.07, CDCl₃); (Found: M⁺, 329.2104, C₁₉H₂₇N₃O₂ requires 329.2103); $\nu_{\max}$ (film)/cm⁻¹ 1637 (C=N); δ_H (200 MHz, CDCl₃) 1.00 (12H, d and t, *J* 7.0 Hz, CH₂CH₃ and CHCH₃), 1.24-1.42 (1H, m, CH₂CH₃), 1.66-1.89 (3H, m, CHCH₃), 4.05-4.14 (1H, apparent t, *J* 13.95, H-5'A), 4.40 (2H, m, H-4'), 4.57-4.66 (1H, dd, *J* 7.85 and 7.95, H-5'B), 7.86 (1H, dd, *J* 8.2, 7.3 Hz, H-4), 8.14 (2H, d, *J* 7.6, H-3, H-5); δ_C (200 MHz, CDCl₃) 22.7 (CH₃), 25.3 (CH₃), 45.4 (CH₂, CH₂CH₃), 65.2 (CH, C-4'), 73.8 (CH₂, C-5'), 125.5 (CH, C-3), 137.3 (CH, C-5), 147.2 (C, C-2), 162.1 (C, C-2'); *m/z* 329 (M⁺, 47%), 314 (M-CH₃, 16%), 286 (314- C=O, 10%), 272 (M-C₄H₉, 100%), 57 (C₄H₉, 9%).

(3*aR,8*bR**)-8-Acetyl-3*a*,8*b*-dihydrofuro-7-hydroxyfuro[3,2-*b*]-benzofuran-2(3*H*)-one (3).**

Preparation of [Cu((*S,S*)-2,6-bis(4-isopropyl-4,5-dihydrooxazol-2-yl)pyridine)](OTf)₂.

Copper(II) triflate (0.31 g), (*S,S*)-(iso-propyl)-pybox **4b** (0.26 g) and 4 Å molecular sieves (ca 1 g) were dried under high vacuum for 45 min. Dry distilled dichloromethane (29 mL) was added to the mixture of solids and the blue solution was stirred under nitrogen at room temperature for 4 h.

Addition of 2-trimethylsilyloxyfuran 1 to 2-acetyl-1,4-benzoquinone 2 using [Cu((S,S)-2,6-bis(4-isopropyl-4,5-dihydro-oxazol-2-yl)pyridine)](OTf)₂ stoichiometrically. 2-Acetyl-1,4-benzoquinone **2** (0.13 g, 0.88 mmol, prepared immediately before use) was added as a solid to the above blue solution of the copper(II) triflate complex and the resulting green mixture was cooled to -100 °C. After 15 min 2-[(trimethylsilyloxy)]furan **1** (0.16 mL) was added over 20 min via a septum and the mixture was allowed to come to room temperature then stirred overnight. The green mixture was transferred to a separating funnel containing aqueous NaHCO₃ (5%, 25 mL) and extracted with dichloromethane (3 x 50 mL). The combined dark reddish-brown extracts were washed with saturated aqueous NaHCO₃ (25 mL), saturated aqueous NaCl (25 mL), and dried (Na₂SO₄). The organic phase was then filtered and the solvents were removed from the filtrate under reduced pressure. Purification of the residue by flash chromatography using hexanes-ethyl acetate (4:1) as eluent afforded the title adduct **3** (0.13 g, 63%) as a yellow solid, m.p. 161-163 °C (lit.²¹ m.p. 164-5 °C); [α]_D²⁰ = -55.6° (c = 0.97, CDCl₃); (Found: M⁺, 234.05282, C₂H₁₀O₅ requires 234.05276); δ _H (400 MHz), 2.80 (3H, s, CH₃), 3.06-3.09 (2H, m, H3), 5.36-5.44 (1H, td, *J* 6.2, 6.2, 2.3 Hz, H3a), 6.29 (1H, d, *J* 6.2 Hz, H8b), 7.04 (1H, d, *J* 9.1 Hz, H6), 7.08 (1H, d, *J* 9.1 Hz, H5), 12.5 (1H, s, OH); δ _C (100 MHz), 30.6 (CH₃), 35.4 (CH₂, C-3), 80.7 (CH, C-3a), 84.3 (CH, C-8b), 116.3 (C, C-8a), 119.6 (C, C-5), 123.4 (CH, C-6), 125.6 (C, C-8), 153.9 (C, C-4a), 158.8 (C, C-7), 173.8 (C, C-2), 203.13 (C=O); *m/z* 234 (M⁺, 83%), 219 (M-CH₃, 100%), 189 (M-COOH, 28%), 175 (219-CO₂, 18%), 43 (MeCO⁺, 28%).

(3aR*,8bR*)-8-Acetyl-3a,8b-dihydrofuro-2-oxofuro-[3,2-*b*]-benzofuran-(3H)-7-yl

(1'S,2'R,5'S)-menthyl carbonate. A sample of the above adduct **3** (0.048 g) in dichloromethane (16 mL) was treated with triethylamine (108 μ L), 4-dimethylaminopyridine (0.011 g) and (+)-menthyl chloroformate (76 μ L). The resultant yellow solution was stirred for 45 min at room temperature under nitrogen, during which time it changed colour to pale orange. The mixture was diluted with dichloromethane (5 mL) and the solution was washed with water (5 mL), aqueous HCl (5 mL, 1 mol L⁻¹) and aqueous NaHCO₃ (5 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. Purification of the residue by flash chromatography using hexanes-ethyl acetate (6:1) as the eluent afforded the menthyl carbonate derivatives (Found: 416.1836, C₂₃H₂₈O₇ requires 416.1835). The enantiomeric excess of the initial adduct **3** was calculated by integration of the signals due to the CH₃CH in the ¹H NMR spectrum, which established that the ratio of the two menthyl carbonate diastereoisomers was 2:1. δ _H (400 MHz, CDCl₃), 0.81 [(0.66x3)H, d, *J* 7.0 Hz, CHCH₃], 0.83 [(0.33x3)H, d, *J* 7.0 Hz, CHCH₃], 0.95 (1H, d, *J* 6.8 Hz, CH(CH₃)₂), 2.61 (1H, s, COCH₃), 2.98 (1H, dd, *J* 19.0, 1.7 Hz, H3), 3.05 (1H, dd, *J* 19.0, 6.3 Hz, H3), 4.58-4.66 (1H, m, H-1'), 5.35-5.42 (1H, td, *J* 6.2, 6.2 and 1.6 Hz, H3a), 6.35 (1H, d, *J* 6.2 Hz, H8b), 7.00 (1H, d, *J* 8.7 Hz, H6), 7.02 (1H, d, *J* 8.7 Hz, H5); *m/z* 416 (M⁺, 0.3%), 372 (M-CH₂(CH₃)₂, 0.2%), 279 (M-C₁₀H₁₇, 1%), 278 (M-C₁₀H₁₈, 1.3%), 261 (278-OH, 1.5%), 234 (C₁₁H₁₈O₅, 93%), 219 (234-CH₃, 21%), 189 (234-COOH, 5%), 83 (C₆H₁₁⁺, 100%).

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