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Use of bis(oxazoline)–metal complexes as chiral catalysts for asymmetric Diels–Alder reactions using 2-acetyl-1,4-naphthoquinone as a dienophile

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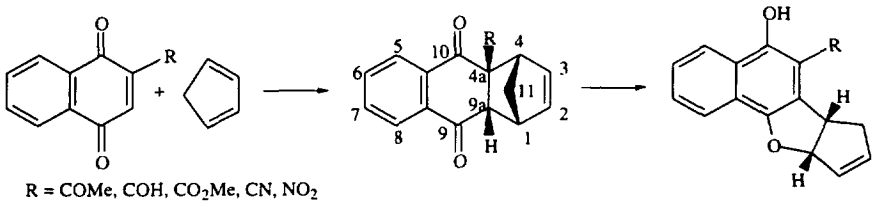
Abstract: Asymmetric Diels–Alder reactions of 1,4-naphthoquinone and 2-acetyl-1,4-naphthoquinone with cyclopentadiene catalyzed by bis(oxazoline)–metal complexes afforded the corresponding Diels–Alder adducts. Moderate levels of enantiomeric excess were obtained and a number of different reaction conditions evaluated. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

The Diels–Alder reaction is one of the most powerful reactions used in organic synthesis for the assembly of a complex array of functionality in a single step.[1] More importantly, development of the regio- and stereochemistry of the Diels–Alder reaction has now been advanced by the tremendous progress made in the development of metal-catalyzed asymmetric variants of Diels–Alder reactions.[2]

The use of quinones as the dienophile component in Diels–Alder reactions has led to the synthesis of interesting cage compounds[3] as well as the synthesis of a range of biologically active natural products.[4] To date asymmetric variants of Diels–Alder reactions using quinones have focused on the use of 5-hydroxy-1,4-naphthoquinone (juglone) as the dienophile. With this latter dienophile the use of enantiopure dienes[5] and enantiopure boron-based[6,7] and titanium-based[8,9] Lewis acids have led to high levels of asymmetric induction.

In the present work we were interested in developing an asymmetric Lewis acid catalyzed Diels–Alder reaction using the quinone dienophiles 3-acetyl-5-hydroxy-1,4-naphthoquinone and 2-acetyl-1,4-naphthoquinone. These latter dienophiles were of particular interest in that the Diels–Alder adducts formed from the addition of cyclopentadiene to 1,4-naphthoquinones bearing electron withdrawing groups at C-2, can undergo selective fragmentation of the C-4–**4a** bond[10] affording an electrophilic site that is then trapped by a hydroxyl group to form a cyclopentannulated product (Scheme 1). Given that any asymmetric induction in the initial Diels–Alder adduct is transferred to the fragmentation product, an avenue for preparing the cyclopentannulated products enantioselectively is herein examined.



R = COMe, COH, CO_2Me, CN, NO_2

Scheme 1.

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Results and discussion

Our initial work focused on the use of Yamamoto's chiral boron reagent derived from trimethyl borate and an (*R*,*R*)-tartaric acid diamide which had afforded Diels–Alder adducts from the reaction of juglone with 1-trimethylsilyloxy-1,3-butadiene in high enantiomeric excess.[6] In order to study the Diels–Alder fragmentation reaction depicted in Scheme 1, the same reaction was carried out using 3-acetyl-5-hydroxy-1,4-naphthoquinone resulting in formation of the Diels–Alder adduct with 18% e.e. The original reaction reported by Yamamoto *et al.*[6] was found to be very specific with respect to the diene and dienophile used, in that the reaction of juglone and 3-acetyl-5-hydroxy-1,4-naphthoquinone with cyclopentadiene afforded the Diels–Alder adducts in high yield with no enantiomeric excess. We next turned to the use of Kelly's chiral boron reagent formed from boron triacetate and (*R*)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-diol[7] which had been successfully used in the Diels–Alder addition of 1-methoxycyclohexa-1,3-diene to juglone. Use of 3-acetyl-5-hydroxy-1,4-naphthoquinone instead of juglone in this reaction afforded the Diels–Alder adduct with no enantiomeric excess. Alternatively use of the Kaufmann catalyst[11] which uses monobromoborane dimethylsulfide and (*R*)-3,3′-diphenyl-1,1′-binaphthalene-2,2′-diol in the Diels–Alder addition of cyclopentadiene to 2-acetyl-1,4-naphthoquinone afforded the adduct with low enantiomeric excess (15% e.e.).

Given the unsuccessful results obtained using chiral boron reagents our attention then focused on the use of chiral titanium(IV) complexes as promoters in the addition of cyclopentadiene to 2-acetyl-1,4-naphthoquinone. Use of Engler's catalyst[8] prepared from $TiCl_4$, $Ti(O^iPr)_4$ and (2*R*,3*R*)-2,3-*O*-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol afforded the adduct with 12% e.e., whereas Mikami's catalyst[9] prepared from $TiCl_2(O^iPr)_2$ and (*R*)-binaphthol afforded the same adduct with no enantiomeric excess. Use of $Yb(OTf)_3$[12] and (*R*)-binaphthol resulted in no enantiomeric excess as did the use of (−)-menthyloxyaluminium dichloride,[13] (−)-8-phenylmenthyloxyaluminium dichloride and (+)-$Eu(hfc)_3$.[14]

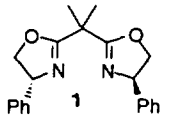
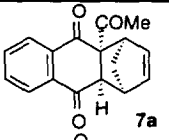
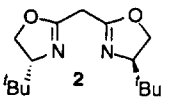
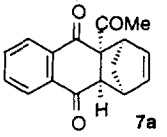
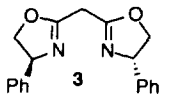
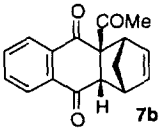
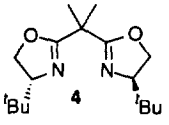
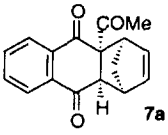
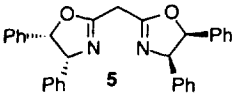
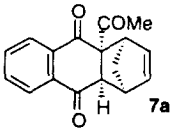
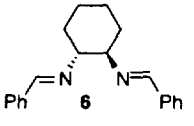
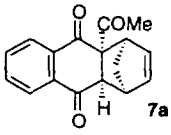
Inspired by the remarkable success obtained by Corey,[15] Evans,[16] Desimoni[17] and Takacs[18] in the asymmetric Diels–Alder addition of cyclopentadiene to α,β-unsaturated *N*-acyloxazolidinones using C_2-symmetric chiral bis(oxazoline)–Mg, –Cu and –Fe catalysts we decided to investigate their use in the addition of cyclopentadiene to 2-acetyl-1,4-naphthoquinones. Reports[19] of highly enantioselective asymmetric hetero Diels–Alder reactions using chiral bis(oxazoline)–Cu catalysts also prompted our use of these catalysts.

Evans' initial work[16b] established that the enantioselectivity obtained in Diels–Alder reactions using α,β-unsaturated *N*-acyloxazolidinones as dienophiles and $Cu(OTf)_2$ is strongly dependent on the nature of the bis(oxazoline) ligand substituent. The efficacy of this two point binding Lewis acid had been demonstrated with α,β-unsaturated *N*-acyloxazolidinones as dienophiles. Hence our initial attention focused on the use of chiral bis(oxazolines) using $Cu(OTf)_2$ in the reaction of cyclopentadiene with the dienophile 2-acetyl-1,4-naphthoquinone which was also able to participate in two point binding to the square planar chiral complex (Table 1).

The Diels–Alder reactions were carried out using 10–20 mol% of $Cu(OTf)_2$/bisoxazoline **1–5** in dichloromethane at −78°C and were complete within 30 minutes. In all cases studied the major *endo* adduct **7** was purified by flash chromatography and the enantiomeric excess of the purified material measured by ^1H NMR using the chiral shift reagent (+)-$Eu(hfc)_3$. Subsequent fragmentation of the adduct **7** using $SnCl_4$ in dichloromethane for 0.25 h at 0°C afforded the fragmented product **8** for which the enantiomeric excess was measured by chiral hplc and found to be in excellent agreement with that measured for the original Diels–Alder adduct **7**.

Given that the best e.e. (albeit 30% e.e.) for the *endo* Diels–Alder adduct **7** was obtained using 4,5-diphenyloxazoline **5**, we then proceeded to examine the use of this ligand with different Lewis acids (Table 2). In the related Diels–Alder reaction of cyclopentadiene with α,β-unsaturated *N*-acyloxazolidinones,[15–18] the nature of the Lewis acid used also strongly influenced the asymmetric

Table 1. Reaction of 2-acetyl-1,4-naphthoquinone **9** with cyclopentadiene using $Cu(OTf)_2$ and chiral bis(oxazolines)

Chiral Ligand	*endo* Adduct[a]	Isolated Yield endo adduct	e.e. (%)[b]
 **1**	 **7a**	60	18
 **2**	 **7a**	52	0
 **3**	 **7b**	31	4
 **4**	 **7a**	51	14
 **5**	 **7a**	66	30
 **6**	 **7a**	70	0

(a) Absolute stereochemistry of endo adduct assigned by assuming a square planar Cu-complex analogous to that used by Evans *et al.*[16a]

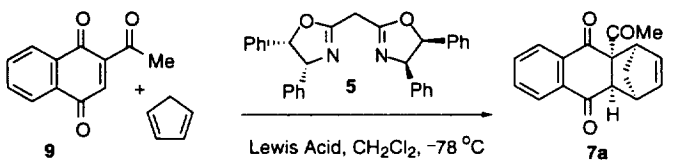
(b) %e.e. of **7** measured by nmr using chiral shift reagent (+)-Eu(hfc)$_3$ and confirmed by chiral hplc (Pirkle Type 1-A column with petrol / isopropanol as eluent) after fragmentation to **8**.

induction in the Diels–Alder reaction. In the present work no enantiomeric excess was observed using $Sn(OTf)_2$, $FeCl_3$, $MgCl_2$ and $ZnCl_2$ suggesting that $Cu(OTf)_2$ was the Lewis acid of choice.

Evans[16c] has uncovered dramatic counterion effects that strongly influence the reactivity of the Lewis acids in Diels–Alder reactions using C_2-symmetric bis(oxazoline)copper(II) complexes. We therefore returned to the use of Cu^{2+} with bisoxazoline **5** and examined the nature of the counterion (Table 3). Use of the non-coordinating counterion SbF_6^- was found to dramatically increase the catalyst efficiency in the the work reported by Evans'[16c] however, in our case this counterion afforded Diels–Alder adducts in low enantiomeric excess. A similar effect was noted using Br^- as the counterion. Use of SbF_6^- and Br^- also afforded a significant quantity of the fragmented product **8** in the initial Diels–Alder reaction.

Having established that the optimum conditions for asymmetric Diels–Alder addition of cyclopentadiene to 2-acetyl-1,4-naphthoquinone **9** involved the use of $Cu(OTf)_2$ with bis(oxazoline) **5**, our attention finally turned to the use of alternative dienes and quinonoid dienophiles (Table 4). Use of 3-acetyl-5-hydroxynaphthoquinone **10** afforded a Diels–Alder adduct **12** with cyclopentadiene in lower enantiomeric excess than that obtained using 2-acetyl-1,4-naphthoquinone **9** whereas the use of juglone **11** in the same reaction afforded an improvement in enantiomeric excess. Use of the dienophile **9** with the acyclic diene, 2,3-dimethyl-1,3-butadiene only afforded the racemic adduct **14**. Addition

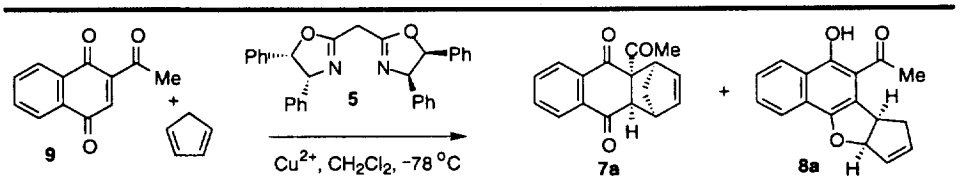
Table 2. Reaction of 2-acetyl-1,4-naphthoquinone **9** with cyclopentadiene using bis(oxazoline) **5** and a Lewis acid



Lewis Acid[a]	7a (%)	e.e. (%)
$Sn(OTf)_2$	60	0
$FeCl_3$	25	0
$MgCl_2$	23	0
$ZnCl_2$	52	0
$Cu(OTf)_2$	66	30

(a) Reactions performed using 20 mol % Lewis acid.

Table 3. Effect of the counterion in the reaction of 2-acetyl-1,4-naphthoquinone **9** with cyclopentadiene using bis(oxazoline) **5** and Cu^{2+}



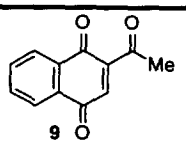
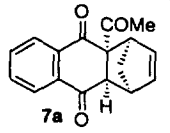
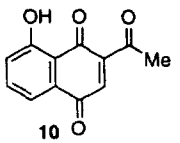
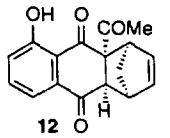
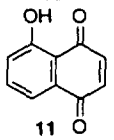
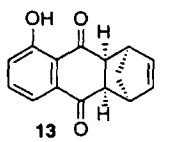
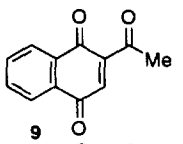
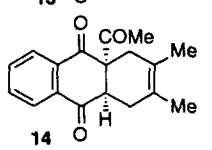
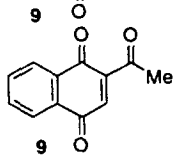
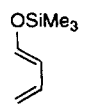
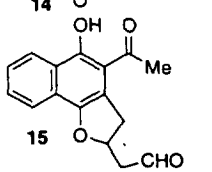
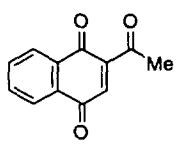
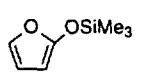
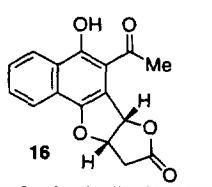
Counter-ion	7a (%)	8a (%)	Total Yield (%)	e.e. (%)[a]
SbF_6^- (Prepared from $CuCl_2$ and $AgSbF_6$)	45	–	45	0
SbF_6^- (Prepared from $CuBr_2$ and $AgSbF_6$)	38	23	61	8
OTf^-	58	8	66	30
Br^-	63	35	98	4

(a) %e.e. of **7** measured by nmr using chiral shift reagent (+)-Eu(hfc)$_3$ and confirmed by chiral hplc (Pirkle Type 1-A column with petrol / isopropanol as eluent) after fragmentation to **8**.

of the silyloxydienes 1-trimethylsilyloxy-1,3-butadiene and 2-trimethylsilyloxyfuran to 2-acetyl-1,4-naphthoquinone **9**, directly afforded the fragmentation products **15** and **16** respectively, with the latter product in low enantiomeric excess.

In summary the work reported herein focuses on the use of bis(oxazoline)–Cu complexes as chiral catalysts for development of asymmetric Diels–Alder additions of dienes to 2-acetyl-1,4-naphthoquinones. To date the enantiomeric excess achieved remains low to moderate, however, the present study represents the initial investigation in this area.

Table 4. Diels–Alder reactions of 1,4-naphthoquinones with dienes in CH_2Cl_2, at −78°C using $Cu(OTf)_2$ and bis(oxazoline) **5**

Quinone	Diene	Adduct	Yield (%)	e.e. (%)
 **9**		 **7a**	66	30[a]
 **10**		 **12**	48	12[b]
 **11**		 **13**	82	50[b]
 **9**		 **14**	20	0
 **9**		 **15**	37	-
 **9**		 **16**	97	10[b]

(a) Determined by nmr using the chiral shift reagent (+)-$Eu(hfc)_3$
(b) Determined by nmr upon conversion to the diastereomeric menthyl carbonates using (-)-menthylchloroformate

Experimental

General details

Melting points were determined using a Reichert–Kofler block and are uncorrected. Infrared absorption spectra were recorded using Perkin–Elmer 1600 Series FTIR spectrometer as Nujol mulls or thin films between sodium chloride plates. ^1H NMR spectra were obtained using either a Bruker AM 400 or Bruker AC 200 spectrometer. ^{13}C NMR data were recorded using a Bruker AM 400 or 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. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) using 1:1 hexane:ethyl acetate as eluent. Bis(oxazolines) **1–5** were obtained from the Aldrich Chemical Co. 2-Acetyl-1,4-naphthoquinone **9**[20] and 3-acetyl-5-hydroxynaphthoquinone **10**[21] were prepared using reported procedures.

(1R,2R)-(+)-N,N′-(Dibenzylidene)-1,2-cyclohexanediamine **6**[16a]

(1*R*,2*R*)-(−)-1,2-Diaminocyclohexane (228 mg, 2.0 mmol) and benzaldehyde (425 mg, 4.0 mmol) were combined in benzene (30 mL) and heated until sufficient water had collected in a Dean–Stark apparatus. The solvent was removed under reduced pressure and the product triturated with hexane to give the title compound as a colourless solid (397 mg, 68%): m.p. 104–106°C; $[\alpha]_D$=−232.6 (*c* 1.46, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40–2.05 (m, 8H, 3-CH_2, 4-CH_2, 5-CH_2 and 6-CH_2), 3.32–3.55 (m, 2H, 1-H and 2-H), 7.26–7.36 (m, 3H, 2′-H, 4′-H and 6′-H), 7.54–7.62 (m, 2H, 3′-H and 5′-H), 8.21 (s, 1H, CH=N); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.5 (t, 4-CH_2 and 5-CH_2), 32.9 (t, 3-CH_2 and 6-CH_2), 73.8 (d, 1-CH and 2-CH), 127.9 (d, 2′-H and 6′-H), 128.4 (d, 3′-H and 5′-H), 130.2 (d, 4′-H), 136.3 (s, 1′-H), 161.1 (d, HC=N); IR (NaCl): 2925, 2855, 1643 (C=N), 1578 (C=C), 1450; m/z (EI) 187, 156, 106, 29; [found: C, 82.5; H, 7.4; N, 9.7. $C_{18}H_{22}N_2$ requires C, 82.7; H, 7.6; N, 9.7%].

Representative procedure for bis(oxazoline)–copper catalysed Diels–Alder reactions of 2-acetyl-1,4-naphthoquinone with cyclopentadiene (20 mol% catalyst) are as follows:

(1R,4S*,4aS*,9aS*)-4a-Acetyl-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthracenedione* **7**

Copper triflate (14.5 mg, 0.04 mmol) and 2,2′-methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] **5** (18.4 mg, 0.04 mmol) were combined under nitrogen and stirred for 4.5 hours at room temperature in dichloromethane (4.0 mL). 2-Acetyl-1,4-naphthoquinone **9**[20] (40 mg, 0.20 mmol) was then added and the mixture was cooled to −100°C. Freshly distilled cyclopentadiene (30 μL) was added dropwise over 5 minutes. After 1 hour the mixture was poured into sodium hydrogen carbonate solution (15 mL) and extracted with dichloromethane (2×10 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product purified by flash chromatography (hexane:ethyl acetate 6:1) to give the title compound **7** as a pale yellow oil (35 mg, 66%): $[\alpha]_D$=+12.9 (*c* 0.54, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (ddd, J=1.3, 1.3, 9.2, 1H, 11-H_B), 1.57 (ddd, J=9.2, 1.5, 1.5, 1H, 11-H_A), 2.36 (s, 3H, COMe), 3.57–3.68 (m, 1H, 1-H), 3.86–3.92 (m, 2H, 9aH and 4-H), 6.08–6.13 (m, 2H, 2-H and 3-H), 7.63–7.75 (m, 2H, 6-H and 7-H), 7.92–8.04 (m, 2H, 5-H and 8-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.2 (q, COMe) 47.0 (t, C-11), 48.1 (d, C-1), 52.9 (d, C-4), 52.9 (d, C-9a), 73.7 (s, C-4a), 126.9 (d, C-3), 127.1 (d, C-2), 134.3 (d, C-6 or C-7), 134.6 (d, C-7 or C-6), 135.2 (s, C-4b or C-8a), 135.3 (s, C-8a or C-4b), 136.5 (d, C-5 or C-8), 138.2 (d, C-8 or C-5), 194.7 (s, C-9 or C-10), 196.5 (s, C-10 or C-9), 203.0 (s, COMe); IR (thin film, NaCl): 1720 (COMe), 1702 (C=O), 1674 (s, C=O), 1591 (C=C); m/z (CI, CH_4) 267 [$(M+1)^+$, 93%], 229 (21%), 201 ([$M-C_5H_6]^+$, 100%); HRMS analysis [$(M+1)^+$ $C_{17}H_{15}O_3$=267.1021] found m/z 267.1021. The enantiomeric excess was determined by 400 MHz ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ shift reagent. The diastereomeric complexes formed were in the ratio of 1:1.86. The enantiomeric excess was therefore determined to be 30%. For the other ligands used refer to Table 1.

(6bR,9aR*)-6-Acetyl-6b,9a-dihydro-5-hydroxy-7H-cyclopenta[b]naphtho[1,2-d]furan* **8**

(1*R**,4*S**,4a*S**,9a*S**)-4a-Acetyl-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthracenedione **7** (26.6 mg, 0.1 mmol) in dichloromethane (5 mL) under nitrogen at 0°C was treated with a catalytic amount of tin(IV) chloride and stirred for 5 minutes. The reaction mixture was then poured into water (5 mL) and extracted with dichloromethane (2×5 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to give a yellow solid. Further purification by flash chromatography (hexane:ethyl acetate 9:1) afforded the title compound **8** as a yellow solid (23 mg, 86%): m.p. 162–163°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.56 (dd, J=17.1, 8.4, 1H, 7-H_B), 2.72 (s, 3H, COMe), 3.08 (dd, J=17.1, 8.4, 1H, 7-H_A), 4.55 (ddd, J=8.4, 8.4, 2.9, 1H, 6b-H), 5.94–6.09 (m, 3H, 9a-H, 8-H and 9-H), 7.49 (dd, J=8.1, 8.1, 1H, 3-H), 7.61 (dd, J=8.1, 8.1 Hz, 1H, 2-H), 7.87 (d, J=8.1, 1H, 4-H), 8.42 (d, J=8.1, 1H, 1-H), 14.3 (s, 1H, 5-OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.1 (q, COMe) 42.5 (t, C-7), 46.8 (d, C-6b), 91.7 (d, C-9a), 121.7 (d, C-8 or C-9), 125.0 (d, C-9 or C-8), 125.4 (s, C-4a or C-11a), 125.6 (s, C-11a or C-4a), 126.0 (d, C-1 or C-4), 129.7 (d, C-4 or C-1),

130.0 (d, C-2 or C-3), 135.2 (d, C-3 or C-2), 157.0 (s, C-5 or C-11), 160.6 (s, C-11 or C-5), 203.3 (s, COMe); IR (NaCl): 1631 (C=O), 1597 (C=C), 1565; m/z (EI) 266 (M+, 78%), 248 (100%), 231, 219, 205, 165 (24%), 115, 105; HRMS analysis ($C_{17}H_{14}O_3$=266.0943) found m/z 266.0951; the optical purity of this compound could be determined by high pressure liquid chromatography, on a Pirkle Type 1-A column, using a hexane:isopropyl alcohol (0.5%) solvent system. The enantiomers had retention times of 60.70 minutes and 64.20 minutes respectively. It was found that the chirality was preserved in the formation of the product, the enantiomeric excess of the title compound being the same (by high pressure liquid chromatography) as that of (1*R**,4*S**,4a*S**,9a*S**)-4a-acetyl-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthracenedione **7** (determined by chiral shift NMR).

(1R,4S*,4aS*,9aS*)-4a-Acetyl-1,4,4a,9a-tetrahydro-5-hydroxy-1,4-methano-9,10-anthracenedione* ***12***

Copper triflate (10.0 mg, 0.027 mmol) and 2,2′-methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] **5** (12.9 mg, 0.028 mmol) were combined under nitrogen and stirred for 4.5 hours at room temperature in dichloromethane (4.0 mL). 3-Acetyl-5-hydroxynaphthoquinone **10**[21] (33 mg, 0.15 mmol) was then added and the mixture was cooled to −100°C. Freshly distilled cyclopentadiene (40 μL) was added dropwise over 5 minutes. After 1 hour the mixture was poured into sodium hydrogen carbonate solution (15 mL) and extracted with dichloromethane (2×10 mL). The solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (hexane:ethyl acetate 6:1) to give the title compound (21 mg, 48%): $[\alpha]_D$=+7.62 (*c* 1.05, CH_2Cl_2); m.p. 136–138°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (ddd, J=9.2, 1.4, 1.4 Hz, 1H, 11-H_B), 1.63 (ddd, J=9.2, 1.6, 1.6, 1H, 11-H_A), 3.60–3.64 (m, 1H, 1-H), 3.74 (d, J=4.0, 1H, 9a-H), 3.90–3.94 (m, 1H, 4-H), 6.11–6.17 (m, 2H, 2-H and 3-H), 7.26 (dd, J=7.6, 1.4, 1H, 6-H), 7.61 (dd, J=7.6, 1.4, 1H, 8-H) 7.63 (dd, J=7.6, 7.6, 1H, 7-H), 12.20 (s, 1H, 5-OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.7 (q, COMe), 47.6 (t, C-11), 48.9 (d, C-1), 52.7 (d, C-4), 53.4 (d, C-9a), 71.6 (s, C-4a), 118.6 (d, C-3), 123.9 (d, C-2), 136.1 (d, C-6), 137.6 (d, C-8), 138.1 (d, C-7), 162.2 (s, C-5), 195.6 (s, C-9 or C-10), 202.3 (s, C-10 or C-9), 203.5 (s, COMe); IR (NaCl) 1706 (C=O, COMe), 1682 (C=O, quinone), 1628, 1577 (C=C), 1471, 1353, 1281; m/z (CI, CH_4) 283 [$(M+1)^+$, 85%], 245 (21%), 217 [$(M-C_5H_6)^+$, 100%], 175, 67. HRMS analysis (M^+ $C_{17}H_{14}O_4$=282.0892) found m/z 282.0910. To determine the enantiomeric excess the adduct was converted to the menthyl carbonate, (1*R*,2*S*,5*R*)-menthyl (1*R**,4*S**,4a*S**,9a*S**)-4a-acetyl-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthracenedione-5-yl carbonate in high yield. ^{1}H NMR analysis at 400 MHz then revealed the presence of two diastereomers in the ratio of 1:1.27. The enantiomeric excess was therefore calculated to be 12%.

(1R,2S,5R)-Menthyl (1R,4S*,4aS*,9aS*)-4a-acetyl-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthracenedione-5-yl carbonate*

(1*R**,4*S**,4a*S**,9a*S**)-4a-Acetyl-1,4,4a,9a-tetrahydro-5-hydroxy-1,4-methano-9,10-anthracenedione **12** (12 mg, 0.043 mmol) in dichloromethane (3 mL) was treated with triethylamine (20 μL) and dimethylaminopyridine (catalytic amount). (−)-Menthyl chloroformate (14 μL) was then added and the mixture stirred for 45 minutes. The volatile components were removed under reduced pressure and the crude product purified by flash chromatography (hexane:ethyl acetate 6:1) to give the title compound as a pale oil (mixture of diastereomers, 16 mg, 69%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75–1.90 (m, 18H, menthyl–H), 2.05–2.39 (m, 2H, 11-H_A and 11-H_B), 3.50–3.65 (m, 2H, 1-H and 4-H), 3.76–3.86 (m, 2H, 4a-H and 9a-H), 4.45–4.69 (m, 1H, 1′-H), 6.10–6.23 (m, 2H, 2-H and 3-H), 7.34–7.45 (m, 1H, 6-H), 7.62–7.76 (m, 1H, 7-H), 7.85–7.96 (m, 1H, 8-H); IR (thin film, NaCl): 2955, 2870, 1760 (COMe), 1682 (C=O), 1596 (C=C), 1456, 1369, 1227; m/z (CI, CH_4) 465 ($[M+1]^+$, 20%), 399 (22%), 327 (32%), 261 (83%), 139 (100%), 67; HRMS analysis ($C_{28}H_{33}O_6$=465.2277) found m/z 465.2277.

(1R,4S*,4aR*,9aS*)-1,4,4a,9a-Tetrahydro-5-hydroxy-1,4-methano-9,10-anthracenedione* ***13***

Copper triflate (10.0 mg, 0.027 mmol) and 2,2′-methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] **5** (12.9 mg, 0.028 mmol) were combined under nitrogen and stirred for 4.5 hours at room temperature in dichloromethane (4.0 mL). Juglone **11** (48 mg, 0.28 mmol) was then added and the mixture was cooled to −100°C. Freshly distilled cyclopentadiene (40 μL) was added dropwise over 5 minutes. After 1 hour the mixture was poured into sodium hydrogen carbonate solution (15 mL) and extracted with dichloromethane (2×10 mL). The solvent was removed under reduced pressure and the residue purified by flash chromatography (hexane:ethyl acetate 6:1) to give the title compound **13** as a pale yellow oil (54 mg, 82%): $[\alpha]_D$=+49.26 (CH_2Cl_2, c=1.08). M.p. 130–132°C (lit.[22] 133–134°C).

To determine the enantiomeric excess the adduct was converted to the menthylcarbonate derivative, (1*R*,2*S*,5*R*)-menthyl (1*R**,4*S**,4a*R**,9a*S**)-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthracenedione-5-yl carbonate in high yield; ^{1}H NMR analysis at 400 MHz then revealed the presence of two diastereomers in the ratio of 1:3.0. The enantiomeric excess of **13** was therefore calculated to be 50%.

(1R,2S,5R)-Menthyl (1R,4S*,4aR*,9aS*)-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthracenedione-5-yl carbonate*

(1*R**,4*S**,4a*R**,9a*S**)-1,4,4a,9a-Tetrahydro-5-hydroxy-1,4-methano-9,10-anthracenedione **13** (27 mg, 0.11 mmol) in dichloromethane (5 mL) was treated with triethylamine (46 μL) and dimethylaminopyridine (catalytic amount). (−)-Menthyl chloroformate (32 μL) was then added and the mixture stirred for 45 minutes. The volatile components were removed under reduced pressure and the crude product purified by flash chromatography (hexane:ethyl acetate 6:1) to give the title compound as a pale oil (44 mg, mixture of diastereomers, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–1.84 (m, 18H, menthyl–H), 2.18–2.39 (m, 2H, 11-H_A and 11-H_B), 3.41–3.49 (m, 2H, 1-H and 4-H), 3.53–3.67 (m, 2H, 4a-H and 9a-H), 4.61–4.76 (m, 1H, 1′-H), 5.92–6.13 (m, 2H, 2-H and 3-H), 7.40 (dd, J=7.8, 1.4, 1H, 6-H), 7.67 (dd, J=7.8, 7.8, 1H, 7-H), 7.92 (dd, J=7.8, 1.4, 1H, 8-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1, 20.8, 22.0, 23.2, 25.9, 31.5, 34.0, 40.5, 46.9, 49.1, 49.4, 49.9, 50.6, 80.1, 125.0, 128.7, 134.3, 135.2, 136.0, 136.2, 138.0, 149.3, 152.7, 196.3, 197.3; IR (thin film, NaCl): 2956, 1758 (C=O), 1682 (C=O), 1595 (C=C), 1455, 1256, 1226; m/z (CI, CH_4) 423 [$(M+1)^+$, 11%], 357 (39%), 285 (20%), 241 (19%), 219 (33%), 175 (46%), 139 (100%), 67; [found: C, 73.6; H, 7.1. $C_{26}H_{30}O_5$ requires C, 73.9; H, 7.2%].

(4aS,9aS*)-4a-Acetyl-1,4,4a,9,9a-tetrahydro-2,3-dimethyl-9,10-anthracenedione* ***14***

Copper triflate (9.0 mg, 0.025 mmol) and (*R*)-(+)-2,2′-isopropylidenebis(4,5-diphenyl-2-oxazoline) **5** (8.8 mg, 0.026 mmol) were combined in dichloromethane (1.5 mL) under nitrogen and stirred for 5 hours at room temperature. After cooling to −78°C, 2-acetyl-1,4-naphthoquinone **9** (50 mg, 0.25 mmol) and 2,3-dimethylbutadiene (41 mg, 0.5 mmol) were added and the mixture was warmed to room temperature and stirred for 3 days. The mixture was washed with sodium hydrogen carbonate solution (5%, 10 mL), dried ($MgSO_4$) and the solvent removed at reduced pressure. The crude product was purified by flash chromatography on silica (hexane:ethyl acetate, 6:1) to give the title compound as a colourless oil (14 mg, 20%) for which no optical rotation was observed; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.59 (s, 3H, 2-Me or 3-Me), 1.73 (s, 3H, 2-Me or 3-Me), 2.13 (s, 3H, COMe), 2.10–2.25 (m, 3H, 1-H_A, 1-H_B and 4-H_A), 2.95–3.12 (m, 1H, 4-H_B), 3.54 (dd, J=8.0, 8.0, 1H, 9a-H), 7.66–7.82 (m, 2H, 6-H and 7-H), 7.96–8.13 (m, 2H, 5-H and 8-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.5 (q, 2-Me or 3-Me), 18.9 (q, 2-Me or 3-Me), 25.6 (q, COMe), 31.9 (t, C-1), 33.9 (t, C-4), 48.8 (d, C-9), 68.4 (q, C-4a), 122.6 (q, C-2 or C-3), 123.7 (q, C-3 or C-2), 126.9 (d, C-6 or C-7), 127.1 (d, C-7 or C-6), 132.7 (q, C-4b or C-8a), 133.5 (q, C-8a or C-4b), 134.1 (d, C-8 or C-5), 135.0 (d, C-5 or C-8), 194.5 (s, C-9 or C-10), 196.8 (s, C-10 or C-9), 204.4 (s, COMe); IR (thin film, NaCl): 2919, 1690 (b, C=O), 1593 (C=C), 1440, 1358, 1280, 1254, 1192; m/z 282 (M^+, 9%), 264 (67%), 239 [$(M-COCH_3)^+$ 100%], 224 (52%), 195, 181, 165, 133 (42%), 43 (68%); HRMS analysis ($C_{18}H_{18}O_3$=282.1256); found m/z 282.1261.

(2R)-4-Acetyl-5-hydroxy-2-(2′-oxoethyl)-2,3-dihydronaphtho[1,2-b]furan* ***15***

Copper triflate (9.0 mg, 0.025 mmol) and (*R*)-(+)-2,2′-isopropylidenebis(4,5-diphenyl-2-oxazoline) **5** (8.8 mg, 0.026 mmol) were combined under argon and stirred for 4.5 hours at room temperature in dichloromethane (1.5 mL). 2-Acetyl-1,4-naphthoquinone **9** (50 mg, 0.25 mmol) was then added, the mixture cooled to −78°C and 1-trimethylsilyloxy-1,3-butadiene (71 μL) added. After 1 hour the solvent was removed and the crude mixture purified by flash chromatography (hexane:ethyl acetate 2:1) to give **15** as a dark yellow oil (25 mg, 37%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H, COMe), 2.92 (dd, J=5.1, 16.5, 1H, 3-H_A), 3.13 (dd, J=5.3, 16.5, 1H, 3-H_B), 3.25 (dd, J=6.3, 15.5, 1H, 1′-H_A), 3.83 (dd, J=9.4, 15.5 Hz, 1H, 1′-H_B), 5.38 (m, 1H, 2-H) 7.51 (dd, J=5.6, 5.6, 1H, 7-H), 7.62 (dd, J=5.6, 5.6, 1H, 8-H), 7.84 (d, J=5.6, 1H, 6-H), 8.42 (d, J=5.6, 1H, 9-H), 9.93 (s, 1H, 2′-CHO), 14.3 (s, 1H, 5-OH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.8 (q, COMe), 40.1 (t, C-3), 49.9 (t, C-1′), 77.0 (d, C-2), 113.8, 121.2, 124.7, 125.0, 125.3, 126.0, 130.1, 157.4, 163.9, 199.8, 203.5; IR (thin film, NaCl): 3420 (b), 1723 (CHO), 1634 (C=O), 1614 (C=O), 1596 (C=C), 1567, 1453; m/z 270 (M^+, 98%), 226 (63%), 211, 181, 152, 115, 105, 77, 43 (100%); HRMS analysis ($C_{16}H_{14}O_4$=270.0892) found m/z 270.0893.

(6bR,9aS*)-6-Acetyl-6b,9a-dihydro-5-hydroxyfuro[3,2-b]naphtho[2,1-d]furan-8(9H)-one* ***16***

Copper triflate (20.0 mg, 0.055 mmol) and 2,2′-methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] **5** (25.8 mg, 0.056 mmol) were combined under nitrogen and stirred for 4.5 hours at room temperature in dichloromethane (5.0 mL). 2-Acetyl-1,4-naphthoquinone **9** (30 mg, 0.15 mmol) was added and the mixture was then cooled to −100°C followed by the addition of 2-trimethylsilyloxyfuran (40 μL). After 1 hour the reaction mixture was warmed to room temperature and then poured into sodium hydrogen carbonate solution (5%, 15 mL). After extraction with dichloromethane (2×10 mL) and drying over $MgSO_4$, the solvent was removed at reduced pressure and the crude product purified by flash chromatography (hexane:ethyl acetate 3:1) to give (6b*R**,9a*S**)-6-acetyl-6b,9a-dihydro-5-hydroxyfuro[3,2-b]naphtho[2,1-d]furan-8(9H)-one **16** as a yellow solid (41 mg, 97%): m.p. 198–200°C (lit.[23] m.p. 197–198°C); $[\alpha]_D$=+42.9 (*c* 0.42, CH_2Cl_2).

To determine the enantiomeric excess the adduct **16** was converted to the menthyl carbonate derivative. ^{1}H NMR analysis at 400 MHz then revealed the presence of two diastereomers in the ratio of 1:1.22. The enantiomeric excess was therefore calculated to be 10%.

[(6bR,9aS*)-6-Acetyl-6b,9a-dihydro-8-oxofuro[3,2-b]naphtho[2,1-d]furan(9H)-5-yl (1R,2S,5R)-menthyl carbonate*

(6b*R**,9a*S**)-6-Acetyl-6b,9a-dihydro-5-hydroxyfuro[3,2-b]naphtho[2,1-d]furan-8(9H)-one **16** (15 mg, 0.053 mmol) in dichloromethane (3 mL) was treated with triethylamine (25 μL) and dimethylaminopyridine (catalytic amount). (−)-Menthyl chloroformate (16 μL) was then added and the mixture stirred for 45 minutes. The volatile components were removed under reduced pressure and the crude product purified by flash chromatography (hexane:ethyl acetate 6:1) to give the title compound as a pale oil (20 mg, mixture of diastereomers, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80–2.20 (m, 18H, menthyl–H), 2.68 (s, 3H, COMe), 3.12–3.17 (m, 2H, 9-H_A and 9-H_B), 4.61–4.70 (m, 1H, 1′-H), 5.55–5.61 (m, 1H, 9a-H), 6.82–6.85 (m, 1H, 6b-H), 7.61–7.70 (m, 2H, 2-H and 3-H), 7.86–7.94 (m, 1H, 4-H), 8.00–8.05 (m, 1H, 1-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2 (q, 5′-Me), 20.7 (q, 2′-CH(CH_3)$_2$), 21.9 (d, 2′-CH(CH_3)$_2$), 23.2 (t, C-4′), 26.4 (d, C-5′), 31.4 (q, COMe), 34.0 (t, C-3′), 35.5 (t, C-9), 40.5 (t, C-6′), 46.9 (d, C-2′), 80.8 (d, C-9a), 82.4 (d, C-1′), 83.9 (d, C-6b), 114.1 (s, C-6), 122.4 (s, C-6a), 122.7 (d, C-4 or C-1), 122.8 (d, C1 or C-4), 123.6 (d, C-2 or C-3), 129.2, (d, C-3 or C-2), 129.3 (s, C-10b or C-4a), 153.1 (s, C-10a), 156.2 (s, C-5), 174.4 (s, C-8), 198.0 (s, COMe); IR (thin film, NaCl): 2956, 1784 (s, C=O), 1764 (s, C=O), 1686 (C=O), 1595 (C=C), 1388, 1243, 1232, 1167; m/z (CI, CH_4) 467 ([M+1]$^+$, 19%), 329 (37%), 285 (100%), 241, 139 (50%), 83; HRMS analysis ($C_{27}H_{31}O_7$=467.1992) found m/z 467.2022.

Acknowledgements

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