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Synthesis of some new enantiopure [2.2]paracyclophanes bearing polycyclic aromatic subunits

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Abstract—The synthesis of some new optically active[2.2]paracyclophanes containing condensed polycyclic aromatic subunits is described. The Diels–Alder reactions of (*S*)-(+)-4-ethenyl[2.2]paracyclophane with 1,4-naphthoquinone, 5-hydroxy-1,4-naphthoquinone and 5,8-dihydroxy-1,4-naphthoquinone have been studied. The effect of the hydroxy group(s) on the reactivity of the dienophiles and on the regioselectivity of the Diels–Alder reaction has been discussed. A structural analysis of the reaction products by ^{1}H and ^{13}C NMR spectroscopy is also presented.

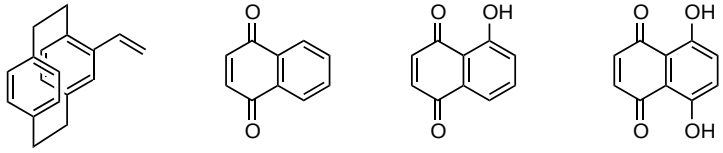
1. Introduction

Recently we have reported an efficient synthesis[1] of (*S*)-(+)-4-ethenyl[2.2]paracyclophane **1** and have shown that the addition of dienophiles to this diene provides an easy entry to enantiopure condensed [2.2]paracyclophanes which are not easily accessible by other methods.[2] Since there is an increasing interest in optically active helicenophanes due to their extraordinary optical properties and potential applications as new materials and chiral ligands, we have extended the study of the Diels–Alder reaction to naphthoquinones in order to synthesize new optically active condensed [2.2]paracyclophanes for future studies. Herein we report the cycloaddition reactions of diene **1** with 1,4-naphthoquinone **2**, 5-hydroxy-1,4-naphthoquinone **3** and 5,8-dihydroxy-1,4-naphthoquinone **4** (Scheme 1) and the conversion of the cycloadducts into optically active helicenophanes.

2. Results and discussion

The Diels–Alder cycloadditions between (*S*)-(+)-4-ethenyl[2.2]paracyclophane **1** and 1,4-naphthoquinones **2**–**4** were examined under different experimental conditions. The best results are summarized in Table 1.

When diene (*S*)-(+)-**1** interacted with 1,4 naphthoquinone **2**, in the presence of trichloroacetic acid, a 1:1.7 mixture of products (*R*)-(−)-**5** and (*S*,*R*)-(+)-**6** was obtained. The highest yield was observed when 1.2 equiv. of naphthoquinone were used. No reaction occurred in the absence of trichloroacetic acid. The reaction products were separated and purified and the structures were assigned by analysis of their ^{1}H and ^{13}C NMR spectra. Whereas compound **5** was the dehydro-derivative of the expected cycloadduct,[3] the major product was surprisingly not derived from a Diels–Alder reaction, but was a Michael-type adduct.[5] Com-



(*S*)-(+)-**1** **2** **3** **4**

Scheme 1.

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Table 1. Reaction conditions[a,b,c] for the Diels–Alder reactions of (*S*)-(+)-4-ethenyl[2.2]paracyclophane **1** with naphthoquinones **2–4**

Reactants (ratio)	Diene conc. (M)	Reaction time (h)	Products (ratio)	Yield (%)
1, **2** (1:1)	0.4	24	**5**, **6** (1:1.7)	48
1, **2** (1:1.2)	0.4	24	**5**, **6** (1:1.7)	57
1, **3** (1:1.1)	0.2	48	Four products	35
1, **4** (1:1)	0.1	48	**10**	17

[a] Solvent: toluene.
[b] All cycloaddition reactions were carried out in the presence of trichloroacetic acid.
[c] Reaction mixture heated at reflux temperature.

pound (*R*)-(−)-**5** was then converted into the aromatic-compound (*R*)-(+)-**7** (Scheme 2) by DDQ oxidation in high yield (98%). The structure of (*R*)-(+)-**7** was assigned on the basis of the well-known outcome of the oxidation reaction and NMR spectroscopic analysis.

The cycloaddition between (*S*)-(+)-**1** and 5-hydroxy-1,4-naphthoquinone **3** afforded a mixture of four products (35%) which could not be separated. The reaction did not occur under thermal conditions.[6] When the product mixture was heated in refluxing toluene in the presence of DDQ, aromatization occurred readily, providing, almost quantitatively (98%), a 2:1 mixture of the regioisomers (*R*)-(+)-**8** and (*R*)-(+)-**9**, respectively, thus indicating the low regioselectivity of the Diels–Alder reaction.

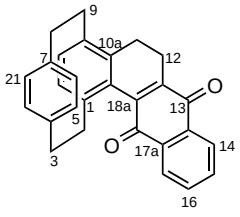
The cycloaddition reaction of diene (*S*)-(+)-**1** with 5,8-dihydroxy-1,4-naphthoquinone **4** in a 0.1 M toluene solution of diene **1** led to product (*R*)-(−)-**10** (17%), which is a dehydroderivative of the cycloadduct. As is usually observed in the cycloadditions of quinones, the primary cycloadducts were partially or totally oxidized under the reaction conditions.[2,4] Again no reaction occurred in the absence of trichloroacetic acid. DDQ oxidation of compound (*R*)-(−)-**10** gave pure (*R*)-(+)-**11** in 98% yield.

The reactions seem to be markedly dependent on the diene concentration and the concentrations reported in Table 1 led to the best yields. It is interesting to point out that hydroxynaphthoquinones are less reactive than naphthoquinone itself. The hydroxy groups modify the reactivity of the naphthoquinones by their electron-donating effect and also by the intramolecular hydrogen bonding which occurs with the carbonyl function, which makes the protonation of the oxygen carbonyl group difficult. Both effects reinforce each other and cause a decrease in the reactivity.[7]

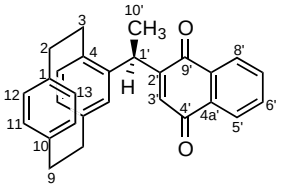
It is also reasonable to hypothesize in this case[2] that each cycloaddition of diene (*S*)-(+)-**1** with dienophiles **2–4** was *anti-endo* diastereoselective, since *syn* addition is hindered by the unsubstituted benzene ring of the paracyclophane moiety.

2.1. Structural analysis

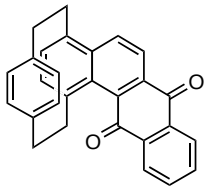
The structural determination of all products is based on the outcome of the reactions used to prepare them and on extensive NMR investigation.



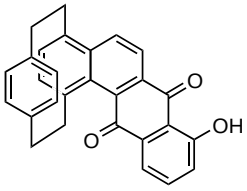
(*R*)-(-)-**5**



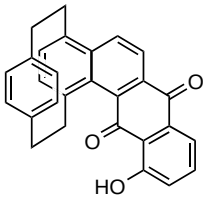
(*S*,*R*)-(+)-**6**



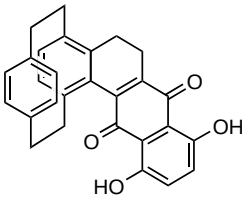
(*R*)-(+)-**7**



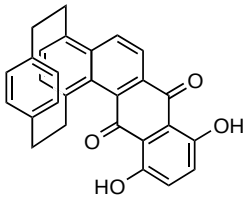
(*R*)-(+)-**8**



(*R*)-(+)-**9**

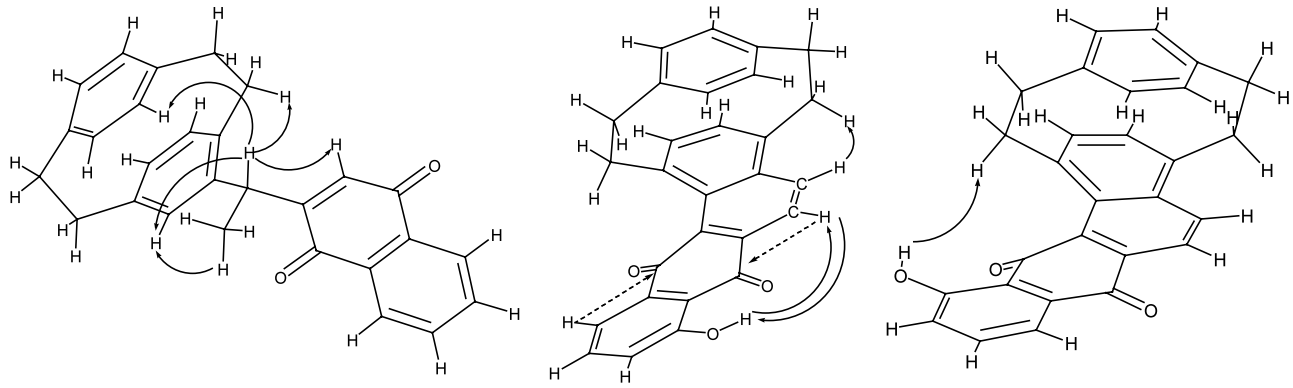


(*R*)-(-)-**10**



(*R*)-(+)-**11**

Scheme 2.



(*S*,*R*)-(+)-**6** (*R*)-(+)-**8** (*R*)-(+)-**9**

Figure 1. Minimized energy conformations of compounds **6**, **8** and **9**; the arrows indicate observed NOEs; dotted arrows indicate long-range hetero-correlations.

Proton and carbon shift assignments follow from the examination of ^{1}H–^{1}H and ^{1}H–^{13}C connectivities (COSY spectra) and from the observed ^{1}H–{^{1}H} NOEs. The configuration of the C(1′) carbon of compound **6** is supported by ^{1}H–{^{1}H} NOESY experiments. Selective pre-irradiation of the C(1′)H resonance resulted in signal enhancement of the resonance attributed to C(3)H, C(3′)H, C(6)H and C(13)H, while saturation of C(1′) methyl protons gave strong enhancement of C(6)H resonance (Fig. 1).

The regiochemistry of the hydroxy function of **8** was established by mutual dipolar contacts observed between C(12)H and C(14)OH, as well as from the long-range hetero-correlations observed between C(18) and C(17)H and between C(13) and C(12)H (Fig. 1).

Furthermore, the NOE effects observed on the resonance of $C(2)H_s$ upon irradiation of the resonance attributed to C(17)OH proton confirmed the regiochemistry of the hydroxy function of **9** (Fig. 1). Finally, for compounds **10** and **11** the structure is confirmed by the NOEs observed on C(6)H, C(9)H and C(12)H upon selective irradiation of the resonance attributed to C(11)H.

3. Conclusions

In summary we have reported the synthesis of some new optically active [2.2]paracyclophanes containing condensed polycyclic aromatic subunits, based on a two-step approach in which the key-step is the Diels–Alder reaction of (*S*)-(+)-4-ethenyl[2.2]paracyclophane **1** with 1,4-naphthoquinones **2**–**4**. The results reported in this paper show that diene **1**, easy available from (*S*)-(+)-4-acetyl[2.2]paracyclophane, is a very useful tool for the synthesis of optically active [2.2]paracyclophanes. The fully aromatized compounds showed high specific rotation values. Further studies along these lines are currently in progress.

4. Experimental

4.1. General

Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ solution on a Jasco DIP-360 polarimeter in a quartz cell at 25°C. GC analyses were performed on a Hewlett–Packard 6890 chromatograph. IR spectra were recorded in $CHCl_3$ solution at room temperature on a Perkin–Elmer Paragon 500 FT IR. NMR spectra were recorded on a Varian Associates VXR-400 multinuclear instrument (internal Me_4Si). The signals with the same apexes in the ^{1}H and ^{13}C spectra may be interchanged. The $[\alpha]_D$ for compounds (*R*)-(−)-**10** and (*R*)-(+)-**11** were determined at very low concentration because they are strongly colored.

4.2. Reaction of diene (*S*)-(+)-1 with 1,4-naphthoquinone 2: synthesis of (*R*)-(−)-′5 and (*S*,*R*)-(+)-6

Trichloroacetic acid (0.200 g, 1.24 mmol) was added to a solution of diene (0.400 g, 1.72 mmol) (*S*)-(+)-**1** and 1,4-naphthoquinone **2** (0.324 g, 2.08 mmol) in toluene (4 mL) and the reaction mixture was heated at reflux temperature for 24 h. The solution was then cooled, diluted with toluene (40 mL), washed with $NaHCO_3$ aqueous solution, dried (Na_2SO_4) and evaporated in vacuo. The residue was then purified on column chromatography (silica gel; eluent: 85:15 hexane/ethyl acetate) to afford pure (*R*)-(−)-**5** as red crystals (0.140 g, 0.36 mmol, 21%) and (*S*,*R*)-(+)-**6** as a yellow microcrystalline solid (0.24 g, 0.60 mmol, 36%).

(*R*)-(−)-**5**: mp 233–234°C (hexane–dichloromethane); $[\alpha]_D = -820$ (*c* 0.096, $CHCl_3$); IR 1660 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 1H, H-11), 2.58 (m, 1H, H-9), 2.79 (m, 1H, H-12), 2.80–3.42 (m, 9H, Hs-2, Hs-3, Hs-8, H-9, H-11, H-12), 6.32[a] (dd, 1H, $J=7.9$, 1.8 Hz, H-5), 6.41[a] (dd, 1H, $J=7.9$, 1.8 Hz, H-6), 6.47 (d, 1H, $J=7.8$ Hz, H-19), 6.51 (d, 1H, $J=7.8$ Hz,

H-20), 6.68[b] (dd, 1H, $J=7.9$, 1.8 Hz, H-21), 6.72[b] (dd, 1H, $J=7.9$, 1.8 Hz, H-22), 7.78 (m, 2H, H-14, H-17), 8.10 (m, 1H, H-15), 8.15 (m, 1H, H-16); ^{13}C NMR ($CDCl_3$) δ 19.7 (C-12), 23.3 (C-11), 32.9, 34.6, 35.2, 37.0 (C-2, C-3, C-8, C-9), 126.0, 126.8 (C-15, C-16), 128.9 (C-18b), 130.6[a] (C-5), 131.2[b] (C-22) 132.5[a] (C-6), 132.2, 132.8 (C-13a, C-17a), 132.9[c] (C-20) 133.4 (C-17), 133.5 (C-14), 133.8[b] (C-21), 134.9 (C-10), 136.9 (C-10a), 137.3[c] (C-19) 139.6 (C-4, C-7), 142.2, 142.3, 142.6 (C-1, C-12a, C-18a), 184.1 (C-13). Anal. calcd for $C_{28}H_{22}O_2$: C, 86.13; H, 5.68. Found: C, 86.3; H, 5.7%.

(*S*,*R*)-(+)-**6**: mp 144–145°C (methanol), $[\alpha]_D=+267$ (*c* 1.100, $CHCl_3$); IR 1663 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3H, $J=7.1$ Hz, Me), 2.68 (m, 1H, H-8), 3.10 (m, 1H, H-8), 3.05–3.25 (m, 6H, Hs-2, Hs-3, Hs-9), 4.43 (dq, 1H, $J=7.1$, 0.9 Hz, CHMe), 6.05 (d, 1H, $J=0.9$ Hz, H-3′), 6.42 (dd, 2H, $J=7.7$, 1.7 Hz, H-6, H-16), 6.44 (dd, 1H, $J=7.8$, 1.9 Hz, H-14), 6.47 (dd, 1H, $J=7.8$, 1.9 Hz, H-12), 6.49 (dd, 1H, $J=7.7$, 1.7 Hz, H-15), 6.53 (dd, 1H, $J=7.8$, 1.9 Hz, H-11), 6.72 (dd, 1H, $J=7.8$, 1.9 Hz, H-13), 7.67–7.76 (m, 2H, H-6′, H-7′), 7.98 (dd, 1H, $J=7.7$, 1.6 Hz, H-8′), 8.16 (dd, 1H, $J=7.7$, 1.6 Hz, H-5′); ^{13}C NMR ($CDCl_3$) δ 18.9 (CH_3), 33.9, 34.2, 35.3 (C-2, C-3, C-9), 34.4 (CHMe), 35.4 (C-8), 126.0 (C-8′), 126.7 (C-5′), 129.1 (C-13), 131.2, 135.5, (C-6, C-16), 131.6 (C-14), 132.0 (C-12), 132.1, 132.2 (C-10, C-11), 133.1 (C-11), 133.5 (C-15), 133.6 (C-7′), 133.7 (C-6′), 135.4 (C-3′), 137.7, 139.4, 139.5, 140.2, 140.5,(C-1, C-4, C-5, C-7, C-10), 157.5 (C-2′), 184.7 (C-9′), 185.2 (C-4′). Anal. calcd for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16; O. Found: C, 85.5; H, 6.3%.

4.3. Synthesis of (*R*)-(+)-7 via oxidation of (*R*)-(−)-5

A solution of compound (*R*)-(−)-**5** (0.400 g, 1.96 mmol) in toluene (44 mL) was treated with DDQ (0.800 g, 3.52 mmol) and heated under reflux for 6 h. The reaction mixture was then evaporated to afford a solid residue, which was purified by column chromatography. Elution with 9:1 hexane/ethyl acetate gave pure (*R*)-(+)-**7** as orange crystals (0.388 g, 1.00 mmol, 98%); mp 255–256°C (hexane/dichloromethane); $[\alpha]_D=+448$ (*c* 0.068, $CHCl_3$); IR 1665 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.73–2.85 (m, 2H, Hs-3), 2.95 (m, 1H, H-8), 3.06 (m, 1H, H-9), 3.17 (m, 1H, H-2), 3.23 (m, 1H, H-8), 3.43 (m, 1H, H-2), 3.83 (m, 1H, H-9), 5.49 (dd, 1H, $J=7.9$, 1.9 Hz, H-5), 5.66 (dd, 1H, $J=7.9$, 1.9 Hz, H-6), 6.59 (dd, 1H, $J=7.9$, 1.9 Hz, H-22), 6.65 (dd, 1H, $J=7.9$, 1.9 Hz, H-21), 6.86 (d, 1H, $J=7.2$ Hz, H-19), 6.98 (dd, 1H, $J=7.2$, 0.9 Hz, H-20), 7.82 (m, 2H, H-15, H-16), 8.19 (d, 1H, $J=8.6$ Hz, H-11), 8.25 (m, 1H, H-14), 8.32 (m, 1H, H-17), 8.33 (d, 1H, $J=8.6$ Hz, H-12); ^{13}C NMR ($CDCl_3$) δ 33.3[a] (C-3), 34.5 (C-8), 35.0[a] (C-9), 37.8 (C-2), 121.6 (C-12), 126.6, 127.8 (C-14, C-17), 128.1 (C-5), 130.3 (C-6), 130.6 (C-11), 130.8[b] (C-10), 131.1 (C-21), 132.4 (C-22), 132.6, 132.7 (C-13a, C-17a), 133.4[c] (C-15), 133.9 (C-18b), 134.2[c] (C-16), 134.8 (C-20), 134.9 (C-19), 135.4[b] (C-1), 135.5[b] (C-10a), 138.0 (C-7), 139.0 (C-12a), 139.1 (C-18a), 140.2 (C-4), 183.8 (C-13), 185.1 (C-18). Anal. calcd for $C_{28}H_{20}O_2$: C, 86.57; H, 5.19. Found: C, 86.4; H, 5.1%.

4.4. Reaction of diene (*S*)-(+)-1 with 5-hydroxy-1,4-naphthoquinone, 3

A toluene solution (12 mL) of **1** (0.600 g, 2.56 mmol), naphthoquinone **3** (0.488 g, 2.80 mmol) and trichloroacetic acid (0.200 g, 1.24 mmol) was heated under reflux for 48 h. The mixture was then worked up as usual. Chromatography on silica gel of the residue, eluting with 95:5 toluene/dichloromethane, gave a mixture of four products (0.372 g, 0.92 mmol, 35%), which was used without further purification in the next step.

4.5. Oxidation of the compounds obtained from the reaction of diene (*S*)-(+)-1 with 5-hydroxy-1,4-naphthoquinone, 3

A toluene solution (20 mL) of the mixture of the compounds derived from the cycloaddition reaction of diene (*S*)-(+)-**1** with 5-hydroxy-1,4-naphthoquinone **3** (0.360 g, 0.88 mmol) was treated with DDQ (0.700 g, 3.08 mmol) in toluene at reflux temperature for 10 h. The residue obtained by evaporating the solvent under reduced pressure was chromatographed using a MERCK Lichoprep Si 60 prepacked column (elution with 98:2 toluene/petroleum ether) to afford pure (*R*)-(+)-**8** (0.234 g, 0.58 mmol, 66%) as red crystals and (*R*)-(+)-**9** as orange crystals (0.114 g, 0.28 mmol, 32%).

(*R*)-(+)-**8**: mp 207–208°C (toluene/petroleum ether); $[\alpha]_D=+219$ (*c* 0.134, $CHCl_3$); IR 1665, 1633 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 2H, Hs-3), 2.95 (m, 1H, H-8), 3.05 (m, 1H, H-9), 3.18 (m, 1H, H-2), 3.24 (m, 1H, H-8), 3.42 (m, 1H, H-2), 3.80 (m, 1H, H-9), 5.54 (dd, 1H, $J=7.9$, 1.9 Hz, H-5), 5.66 (dd, 1H, $J=7.9$, 1.9 Hz, H-6), 6.60 (dd, 1H, $J=7.9$, 1.9 Hz, H-22), 6.66 (dd, 1H, $J=7.9$, 1.9 Hz, H-21), 6.86 (d, 1H, $J=7.3$ Hz, H-19), 6.97 (d, 1H, $J=7.3$ Hz, H-20), 7.31 (dd, 1H, $J=8.3$, 1.3 Hz, H-15), 7.70 (dd, 1H, $J=8.3$, 7.5 Hz, H-16), 7.76 (dd, 1H, $J=7.5$, 1.3 Hz, H-17), 8.12 (d, 1H, $J=8.7$ Hz, H-11), 8.33 (d, 1H, $J=8.7$ Hz, H-12), 12.43 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 33.3 (C-9), 34.5 (C-8), 35.1 (C-3), 37.7 (C-2), 115.4 (C-13a), 119.2 (C-17), 120.9 (C-12), 123.4 (C-15), 128.2 (C-5), 130.5 (C-6), 130.6 (C-11), 131.0 (C-10), 131.1 (C-21), 132.0 (C-18b), 132.4 (C-22), 134.9 (C-20), 135.0 (C-10a), 135.2 (C-19), 135.4 (C-1), 135.5 (C-17a), 136.7 (C-16), 138.0 (C-7), 139.1 (C-12a), 139.4 (C-18a), 140.4 (C-4), 161.8 (C-14), 184.7 (C-18), 189.0 (C-13). Anal. calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98. Found: C, 83.0; H, 5.0%.

(*R*)-(+)-**9**: mp 293–294°C (toluene/petroleum ether); $[\alpha]_D=+186$ (*c* 0.199, $CHCl_3$); IR 1664, 1634 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.78 (m, 1H, H-3), 2.92 (m, 1H, H-3), 2.95 (m, 1H, H-8), 3.08 (m, 1H, H-9), 3.12 (m, 1H, H-2), 3.26 (m, 1H, H-8), 3.55 (m, 1H, H-2), 3.83 (m, 1H, H-9), 5.54 (dd, 1H, $J=8.0$, 1.9 Hz, H-5), 5.63 (dd, 1H, $J=8.0$, 1.9 Hz, H-6), 6.63 (dd, 1H, $J=7.9$, 1.9 Hz, H-22), 6.69 (dd, 1H, $J=7.9$, 1.9 Hz, H-21), 6.86 (d, 1H, $J=7.2$ Hz, H-19), 6.98 (d, 1H, $J=7.2$ Hz, H-20), 7.34 (dd, 1H, $J=8.3$, 1.2 Hz, H-16), 7.68 (t, 1H, $J=8.3$ Hz, H-15), 7.85 (dd, 1H, $J=8.3$, 1.2 Hz, H-14), 8.12 (d, 1H, $J=8.6$ Hz, H-11), 8.32 (d, 1H,

$J=8.6$ Hz, H-12), 12.42 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 33.5 (C-9), 34.6 (C-8), 35.3 (C-3), 38.1 (C-2), 116.9 (C-17a), 119.0 (C-14), 121.6 (C-12), 124.4 (C-16), 128.2 (C-5), 130.6 (C-10), 130.7 (C-6), 130.9 (C-21), 131.4 (C-11), 131.9 (C-18b), 132.6 (C-22), 132.7 (C-13a), 133.2 (C-10a), 134.7 (C-20), 135.2 (C-19), 135.4 (C-1), 136.1 (C-15), 138.1 (C-7), 139.1 (C-18a), 139.6 (C-12a), 140.3 (C-4), 161.6 (C-17), 183.4 (C-13), 189.3 (C-18). Anal. calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98. Found: C, 83.1; H, 5.0%.

4.6. Reaction of diene (*S*)-(+)-1 with 5,8-dihydroxy-1,4-naphthoquinone, 4

A toluene solution (18 mL) of diene **1** (0.400 g, 1.72 mmol), naphthoquinone **4** (0.328 g, 1.72 mmol) and trichloroacetic acid (0.200 g, 1.24 mmol) was heated under reflux for 48 h. After usual work up, the crude product was purified by preparative HPLC (mobile phase: CH_3CN/H_2O 3:2; flow rate: 40 mL/min) to give pure (*R*)-(−)-**10** as violet crystals (0.120 g, 0.28 mmol, 17%); mp 205–206°C (dec.); $[\alpha]_D=-844$ (c $1.2.10^{-3}$, $CHCl_3$); IR 1603 (s, C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 1H, H-11), 2.63 (m, 1H, H-2), 2.80 (m, 1H, H-12), 2.83 (m, 1H, H-9), 2.85 (m, 1H, H-3), 3.00 (m, 1H, H-3), 3.04 (m, 1H, H-8), 3.05 (m, 1H, H-11), 3.25 (m, 1H, H-8), 3.30 (m, 1H, H-2), 3.33 (m, 1H, H-12), 3.40 (m, 1H, H-9), 6.32 (dd, 1H, $J=7.9$, 1.6 Hz, H-6), 6.38 (dd, 1H, $J=7.9$, 1.7 Hz, H-5), 6.47 (d, 1H, $J=7.7$ Hz, H-19), 6.52 (d, 1H, $J=7.7$ Hz, H-20), 6.71 (dd, 1H, $J=7.8$, 1.7 Hz, H-22), 6.74 (dd, 1H, $J=7.8$, 1.6 Hz, H-21), 7.25, 7.27 (bs, 2H, H-15, H-16), 12.60 (s, 1H, OH), 12.75 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 19.5 (C-12), 23.2 (C-11), 32.9 (C-9), 34.6 (C-8), 35.2 (C-3), 37.0 (C-2), 112.0, 112.1 (C-13a, C-17a), 127.9 (C-18b), 129.5, 129.7 (C-15, C-16), 130.7 (C-6), 131.0 (C-21), 132.5 (C-5), 132.7 (C-20), 133.9 (C-22), 134.7 (C-10), 137.0 (C-1), 137.6 (C-19), 139.5, 139.7 (C-4, C-7), 142.4 (C-18a), 142.5 (C-12a), 143.7 (C-10a), 158.6, 159.1 (C-14, C-17), 184.8 (C-13), 185.5 (C-18). Anal. calcd for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.8; H, 5.2%.

4.7. Oxidation of (*R*)-(−)-10

A toluene (20 mL) solution of (*R*)-(−)-**10** (0.400 g, 0.96 mmol) and DDQ (0.800 g, 3.52 mmol) was heated under reflux for 6 h. The reaction mixture was then evaporated under vacuum to afford a solid residue, which was chromatographed on silica gel. Elution with 9:1 hexane/ethyl acetate afforded pure (*R*)-(+)-**11** (0.376 g, 0.88 mmol, 98%) as red crystals; mp 272°C (dec.); $[\alpha]_D=+1193$ (c 0.015, $CHCl_3$); IR 1601 (s, C=O) cm^{-1}; ^{1}H NMR (DMSO) δ 2.72 (m, 1H, H-3), 2.82 (m, 1H, H-3), 2.95(m, 1H, H-9), 2.98 (m, 1H, H-8), 3.08 (m, 1H, H-2), 3.18 (m, 1H, H-8), 3.42 (m, 1H, H-2), 3.82 (m, 1H, H-9), 5.51 (dd, 1H, $J=7.9$, 1.9 Hz, H-5), 5.54 (dd, 1H, $J=7.9$, 1.9 Hz, H-6), 6.60 (dd, 1H, $J=7.8$, 1.9 Hz, H-22), 6.68 (dd, 1H, $J=7.8$, 1.9 Hz, H-21), 6.88 (d, 1H, $J=7.1$ Hz, H-19), 6.98 (d, 1H, $J=7.1$ Hz, H-20), 7.36, 7.38 (bs, 2H, H-15, H-16), 8.25 (d, 1H, $J=8.6$ Hz, H-11), 8.27 (d, 1H, $J=8.6$ Hz, H-12), 12.44 (s, 1H, OH), 12.62 (s, 1H, OH); ^{13}C NMR (DMSO) δ 33.1 (C-9), 34.3 (C-8), 34.9 (C-3), 37.8 (C-2), 112.7, 113.7 (C-13a, C-17a), 120.9 (C-12), 128.3 (C-5), 128.7, 129.5 (C-15, C-16), 130.4 (C-10), 130.8 (C-6), 131.0 (C-21), 131.8 (C-11), 132.0 (C-18b), 132.7 (C-22), 132.8 (C-10a), 134.8 (C-20), 135.4 (C-19), 135.6 (C-1), 138.2 (C-7), 139.1 (C-12a), 139.4 (C-18a), 140.8 (C-4), 156.1, 156.5 (C-14, C-17), 187.3 (C-13), 187.6 (C-18). Anal. calcd for $C_{28}H_{20}O_4$: C, 79.98; H, 4.75. Found: C, 79.8; H, 5.2%.

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