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Asymmetric Synthesis of Rubiginones A_2 and C_2 and Their 11-Methoxy Regioisomers

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Abstract: Convergent enantioselective syntheses of angucyclinone-type natural products rubiginones A_2 (**2**) and C_2 (**1**) and their 11-methoxy regioisomers **3a** and **3b** have been achieved by using two domino processes from a common enantiomerically pure 1-vinylcyclohexene **4**. Key steps in the synthesis of this diene were the stereoselective conjugate addition of $AlMe_3$ on (S*S*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinol (**9**) and the elimination of the β-hydroxy sulfoxide fragment, after oxidation to sulfone, to recover a carbonyl group. The first domino sequence comprised Diels–Alder reaction with a sulfinyl naphthoquinone followed by sulfoxide elimination. An efficient opposite regioselection in the cycloaddition step was achieved in the convergent construction of the tetracyclic skeleton using a sulfoxide at C-2 or C-3 of the dienophiles **5** or **6**, derived from 5-methoxy-1,4-naphthoquinone. The second domino process, triggered by oxygen and sunlight, allowed the transformation of the initial tetracyclic adducts into the final products after B ring aromatization, silyl deprotection and C-1 oxidation.

Keywords: antibiotics · asymmetric synthesis · cycloaddition · natural products

Introduction

Angucyclines and their aglycones, the angucyclinones, are a large group of naturally occurring quinones isolated from the culture broths of different microorganims.[1] All members of the family share a benz[*a*]anthracenequinone framework of decaketide origin,[2] bearing an alkyl (methyl or ethyl) group at C-3 and oxygen functionalities at C-1 and C-8. Most of them show a broad range of biological properties including anticancer, antibacterial and antiviral activity, or enzyme and platelet aggregation inhibition. Their challenging structure and biological interest have stimulated many synthetic studies on both racemic[3,4] and enantioselective[3,5] forms. In spite of the important advances reached, efficient syntheses of these products are still necessary due to the low yields obtained from microorganisms. New chemical syntheses also allow the access to modified analogues with improved biological properties.

Rubiginones are a family of these natural products that have been isolated from the fermentation broth of *Streptomyces griseorubiginosus*.[6] They show the common structural features of all angucyclinones and, in the case of rubiginones A and C, an extra stereogenic oxygenated group at C-4 (Figure 1). They have shown potency of vincristine-induced cytotoxicity against multi-drug-resistant tumor cells.[6] In addition, rubiginone A_2, also named fujianmycin B[7] or SNA-8073-B,[8] was claimed to be useful in the treatment of AIDS and Alzheimer's disease.[9] The absolute stereochemistry of all rubiginones, shown in Figure 1, has been determined by the *O*-methyl mandelate method.[10]

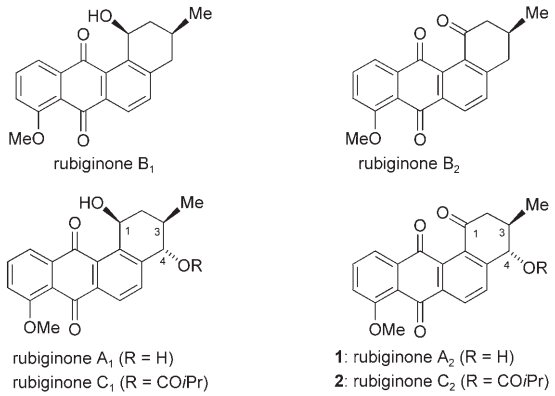

Figure 1. Structures of rubiginones A–C.

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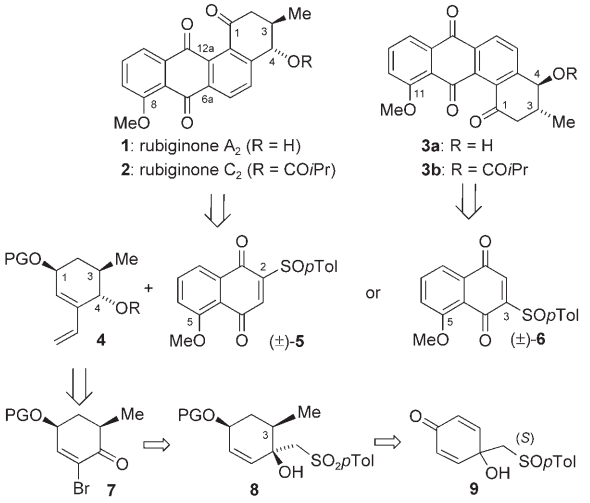
The main problems emerging when planning the synthesis of the angucyclinones are the regioselective construction of the angularly fused tetracyclic skeleton and the stereoselective introduction of the different stereogenic centers. Both have been addressed by several methods which are summarized in different review articles.[3] Among them, the Diels–Alder reaction between a juglone derivative (5-hydroxy-1,4-naphthoquinone) and a vinyl cyclohexene, appears to be the most widely used strategy for the synthesis of the angucyclinone-type structures. In this case, the regioselective formation of the angular skeleton is highly reliant on the substituents present in the naphthoquinone dienophiles. The asymmetric version of these cycloadditions also allowed the access to enantiopure derivatives.[11]

In 1999, we reported the asymmetric total synthesis of (+)-rubiginone B_2 and (+)-ochromycinone,[12] through the [4+2] cycloaddition of enantiomerically pure sulfinyl naphthoquinones, as chiral dienophiles, and racemic chiral vinyl cyclohexenes, as dienes. The strategy used was based on the ability of the sulfoxide to control the π-facial diastereoselectivity of *endo* cycloadditions of sulfinylquinones.[13] Moreover, the sulfinyl group triggered an efficient domino[14] process where the Diels–Alder reaction was followed by the elimination of the sulfoxide, that allowed to recover the quinone moiety in the resulting adduct. When the Diels–Alder reaction was run with a chiral racemic diene,[15] the enantiopure (S*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone promoted a double asymmetric induction process leading to the efficient kinetic resolution of the diene. As a result, using adequately substituted dienes, a one-pot enantioselective formation of the angucyclinone framework[16] occurred. The process was shown to be applicable to a wide range of 1-vinylcyclohexene derivatives.[17]

Abstract in Spanish: *La síntesis enantioselectiva convergente de los productos naturales de tipo anguciclinona, rubiginonas A_2 (**1**) y C_2 (**2**), así como de sus regioisómeros C-11 metoxi sustituidos, **3a** y **3b**, se ha descrito aplicando dos procesos dominó a partir del 1-vinilciclohexeno enantioméricamente puro **4**. Las etapas clave en la síntesis de este dieno han correspondido a la adición conjugada estereoselectiva de $AlMe_3$ sobre el (S*S*)-[p-(tolilsulfinil)metil]-p-quinol (**9**) y a la eliminación del fragmento de β-hidroxi sulfóxido, después de oxidarlo a sulfona, para recuperar un grupo carbonilo. La primera secuencia dominó tuvo lugar mediante una reacción de Diels–Alder con una sulfinil naftoquinona seguida de la eliminación del sulfóxido. La regioselectividad en la etapa de cicloadición que conduce al esqueleto tetracíclico se ha controlado de forma muy efectiva por el sulfóxido existente en las posiciones 2 o 3 de los filodienos **5** y **6**, derivados de la 5-metoxi-1,4-naftoquinona. El segundo proceso dominó, promovido por el oxígeno y la luz solar, permitió la transformación de los aductos tetracíclicos iniciales en los correspondientes productos finales tras la aromatización del anillo B, desprotección del grupo sililo y oxidación del carbono 1.*

Based on this Diels–Alder strategy, we also achieved the enantioselective total synthesis of rubiginones A_2 (**1**) and C_2 (**2**),[18] bearing the additional C-4 oxygenated function (Scheme 1), using an enantiopure vinyl cyclohexene derivative as the source of chirality. Since the absolute configuration at C-1, C-3 and C-4 stereogenic centers[19] was already in the diene moiety, the regioselective construction of the characteristic angular four-ring framework was later achieved by Diels–Alder reaction with racemic 5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**5**) as dienophile. The regiocontrol of the cycloaddition was warranted by the sulfoxide **5**, which also facilitated the formation of the quinonic C_{6a}–C_{12a} double bond by spontaneous elimination, once the tetracyclic skeleton was generated.



Scheme 1. Retrosynthesis of rubiginones A_2 (**1**) and C_2 (**2**) and their 11-methoxy regiosomers **3a** and **3b**.

With the aim of validating the role of the sulfoxide as a regiochemical controller, we decided to investigate the application of this strategy to the synthesis of the 11-methoxy regioisomers of rubiginones A_2 and C_2, compounds **3a** and **3b** (Scheme 1). In this paper we report the synthesis of these analogues, taking advantage of the regiocontrolled Diels–Alder reaction occurring when 5-methoxy-3-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**6**) was used as the dienophile. Our previous work, leading to the synthesis of natural rubiginones A_2 and C_2, is also discussed in full detail, including results not described in our earlier communication.

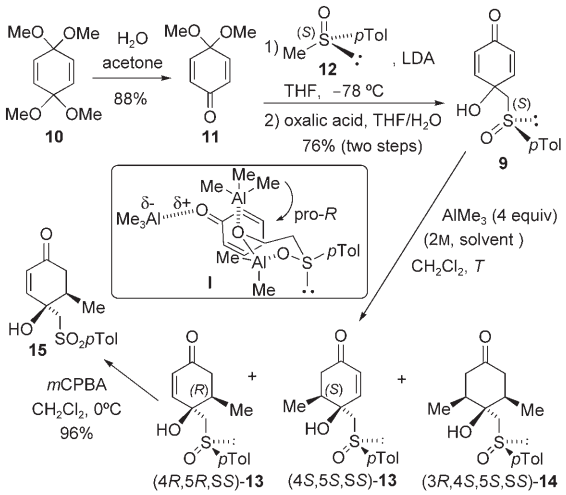
Synthetic plan: The retrosynthesis for compounds **3a** and **3b**, the C-11-methoxy regioisomer of rubiginones A_2 and C_2 (Scheme 1), anticipated the use of a Diels–Alder reaction between 5-methoxy-3-(*p*-tolylsulfinyl)-1,4-naphthoquinone [(±)-**6**] and chiral vinyl cyclohexene **4**. The regioselective construction of the tetracyclic skeleton will be reliant on the ability of the sulfoxide to exert an efficient regiocontrol in the cycloaddition step. The key diene **4**, bringing the final stereogenic centers, is a common intermediate which also allowed the synthesis of natural rubiginones A_2 (**1**) and C_2 (**2**)

using regioisomeric 5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone [(±)-**5**], as the dienophilic partner.

The synthesis of diene **4** was inspired by two pivotal observations dealing with the reactivity of (S*R*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinols. First, the efficient and highly diastereoselective conjugated addition of organoaluminum reagents to the prochiral dienone moiety of (S*R*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinols,[20,21] allowed to envisage this process for the introduction of the C-3 methyl substituent of **4**.[19] Starting from (S*R*)-*p*-quinols, aluminum reagents gave rise to conjugate addition products resulting in the exclusive formation of a new β-alkyl substituted stereogenic center with the (*S*) absolute configuration. We had also shown that the β-hydroxy sulfoxide moiety present at C-4 in the resulting (5*S*,S*R*)-5-alkyl-4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2-cyclohexenones was masking a carbonyl group, which could be liberated upon simple oxidation to sulfone and retroaddition in basic medium.[22] All these features suggested the retrosynthesis shown in Scheme 1 for the preparation of the vinyl cyclohexene **4**. The vinyl group could proceed from a Pd-catalyzed coupling on bromocyclohexenone **7**, whereas the OR substituent at C-4[19] could be derived from a stereoselective reduction of the precursor **7**, in turn available from **8**, after elimination of the β-hydroxy sulfone in a retroaddition process. Taking into account the known stereochemical pathway of AlR_3 conjugate additions on our [(*p*-tolylsulfinyl)methyl]-*p*-quinols,[20,22] the required final (3*R*) absolute configuration of the methyl-bearing chiral center of **8**, would be available from [(*p*-tolylsulfinyl)methyl]-*p*-quinol **9** with the (*S*) absolute configuration at sulfur.

Results and Discussion

The synthesis of enantiopure diene **4** began with 3,3,6,6-tetramethoxy-1,4-cyclohexadiene (**10**),[23] which was subjected to a controlled monohydrolysis with a mixture of acetone/water 10:1 affording the dimethyl monoketal of *p*-benzoquinone (**11**)[24] in 88% yield (Scheme 2). (S*S*)-[(*p*-Tolylsulfinyl)methyl]-*p*-quinol (**9**) was synthesized following the procedure reported for the (S*R*)-enantiomer,[25] by reaction of 4,4-dimethoxy-2,5-cyclohexadienone (**11**) with the lithium anion derived from (S*S*)-methyl-*p*-tolylsulfoxide **12**,[26] followed by ketal hydrolysis with aqueous oxalic acid, in 76% overall yield. The stereoselective conjugated addition of $AlMe_3$ on **9** was conducted successfully after an optimization study (Scheme 2, Table 1). When a CH_2Cl_2 solution of (S*S*)-**9** was added over a commercially available toluene solution of $AlMe_3$ (4 equiv) at −78 °C, a 64:4:32 mixture of (4*R*,5*R*,S*S*)-**13**, (4*S*,5*S*,S*S*)-**13**, and (3*R*,4*S*,5*S*,S*S*)-**14** was formed (entry 1). Diastereoisomers (4*R*,5*R*,S*S*)-**13** and (4*S*,5*S*,S*S*)-**13** resulted, respectively, from attack of $AlMe_3$ to the pro-*R* and pro-*S* conjugate positions of **9**, whereas derivative (3*R*,4*S*,5*S*,S*S*)-**14** was obtained after a double conjugate addition of $AlMe_3$ on both dienone moieties of **9**. Working at lower temperatures (−100 °C), a slight increase of the diastereoselectivity in favor of the desired mono-addition product (4*R*,5*R*,S*S*)-**13** was observed, being only a 2% of the (4*S*,5*S*,S*S*)-**13** diastereomer formed, together with a 28% of the double addition product **14** (entry 2). The best results were achieved after a laborious investigation, which allowed to establish that the temperature and the solvent of the commercially available $AlMe_3$ were the most critical factors to the success of this reaction. Thus, performing the reaction by adding a CH_2Cl_2 solution of the (S*S*)-*p*-quinol **9** at −78 °C over a heptane solution of $AlMe_3$ (4 equiv), the diastereomer (4*R*,5*R*,S*S*)-**13** was exclusively detected and was isolated pure in 65% yield (entry 3).



Scheme 2. Synthesis of β-hydroxy sulfone **15** from *p*-benzoquinone dimethyl bisketal **10**.

Table 1. Addition of Me_3Al to dienone **9** under different experimental conditions.

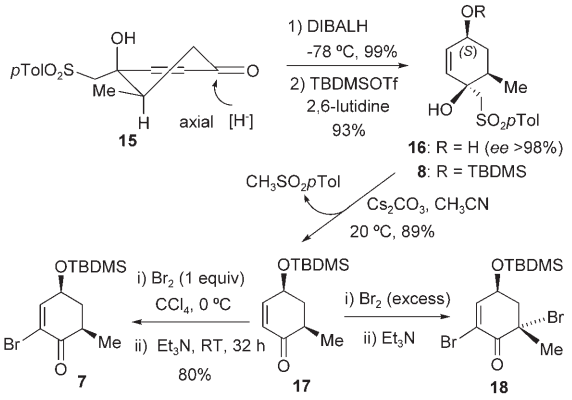
Entry	Solvent	*T* [°C]	(4*R*,5*R*,S*S*)-**13**	(4*S*,5*S*,S*S*)-**13**	**14**
1	toluene	−78	64	4	32
2	toluene	−100	64	2	28
3	heptane	−78	100 (65% yield)	0	0

The highly chemoselective and π-facial diastereoselective formation of compound (4*R*,5*R*,S*S*)-**13** could be explained according with the model already proposed for the analogue reaction on the (S*R*) enantiomer of *p*-quinol **9**.[20b] Thus, the first equivalent of $AlMe_3$ must react with the quinol **9** to form an aluminum alkoxide bearing the spirane-like structure shown in the intermediate **I** (Scheme 2). In such a structure, the aluminum atom of the alkoxide must be associated with the sulfinyl oxygen giving a species which adopts a frozen chair-like conformation due to the presence of the bulky *p*-tolyl group, situated in the equatorial position. In this arrangement, the axial methyl group linked to the aluminum atom is hindering the pro-*S* double bond to the nucleophile approach from the face containing the alkoxide group, rendering only the pro-*R* conjugate position accessible. A second $AlMe_3$ equivalent must be associated to the carbonyl group thus increasing the electrophilicity of the whole dienone system. The high reactivity observed for the $AlMe_3$ conjugate addition, can be due to the intramolecular

transfer assisted by the alkoxide of a third equivalent, as shown in Scheme 2 for intermediate **I**.[27] The use of an excess of $AlMe_3$ reagent warrants the quick completion of the reaction with this reagent, which otherwise is a poor reactive for 1,4-conjugate additions.[20]

En route to the vinyl cyclohexene **4**, we next transformed the sulfoxide group of (4*R*,5*R*,S*S*)-**13** into the sulfone **15** by oxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) in 96% yield (Scheme 2).

The stereoselective reduction of the carbonyl group of cyclohexenone **15**, was accomplished with DIBALH, which afforded carbinol (4*S*)-**16** in almost quantitative yield (Scheme 3). The *S* absolute configuration of the new stereo-

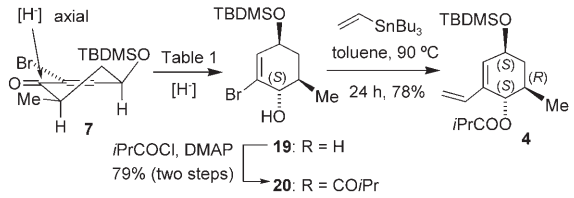


Scheme 3. Synthesis of bromocyclohexenone **7** from β-hydroxy sulfone **15**.

genic center as well the optical purity of **16** was confirmed by further conversion into the corresponding Mosher's esters.[28] The high stereoselectivity observed in this reduction could be a consequence of the rigid half-chair conformation of **15**, shown in Scheme 3, where both, the (*p*-tolylsulfonyl)methyl substituent and the C-5 methyl group, are situated in the most favored equatorial dispositions. In such a conformation, the axial attack of the small hydride DIBALH is favored both from steric and stereoelectronic points of view.[29]

Protection of the resulting carbinol **16** as the TBDMS ether **8** (TBDMSOTf, 2,6-lutidine, 93%), was necessary since all trials to eliminate the β-hydroxysulfone in **16** were unsuccessful. The next step was the transformation of the β-hydroxysulfone moiety of **8** into a carbonyl group by a retroaddition process to eliminate methyl *p*-tolylsulfone. This reaction was carried out by treatment of **8** with Cs_2CO_3 in acetonitrile at room temperature. Under these conditions, enantiopure cyclohexenone **17** was isolated in 89% yield. Slow addition of a CCl_4 solution of bromine at 0°C over **17**, followed by subsequent treatment with Et_3N, led to α-bromoenone **7** in 80% yield. This transformation must occur through the intermediate formation of a non-isolated dibromide suffering the elimination of HBr promoted by Et_3N. The amount of Br_2 added to **17** should be stoichiometric since an excess of Br_2 produced the additional bromination of the α-position at C-6 of **17**, rendering **18**. This undesired product was formed as a unique diastereoisomer in an almost quantitative conversion (Scheme 3).[30]

In accordance with the stereochemistry of the final natural products, the stereochemical course of the reduction of the carbonyl group of bromoenone **7** had to be controlled in order to generate alcohol (1*S*)-**19** with the correct absolute configuration in a highly diastereoselective way. The most stable conformer of **7** must situate both Me and OTBDMS substituents in the pseudoequatorial disposition (Scheme 4).



Scheme 4. Stereoselective reduction of bromocyclohexenone **7** and synthesis of enantiopure vinylcyclohexene **4**.

A small hydride, favoring the axial approach to the carbonyl group,[29] would be adequate. We therefore checked different reagents such as $LiAlH_4$, DIBALH and AlH_3. In all cases, the reduction of **7** was highly diastereoselective giving rise to the expected carbinol (1*S*)-**19**, which resulted from the axial attack of the hydride, together with some amount of the corresponding epimer (1*R*)-**19** (Table 2). The tempera-

Table 2. Reduction of ketone **7** under different experimental conditions.

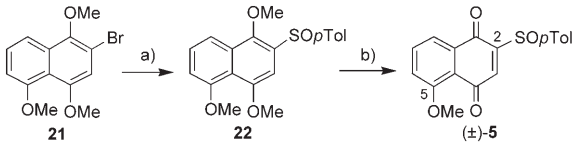
Entry	Hydride	*T* [°C]	Addition[a]	(1*S*)-**19**	(1*R*)-**19**
1	$LiAlH_4$	−78	direct	88	12
2	$LiAlH_4$	−100	direct	93	7
3	$LiAlH_4$	−100	inverse	90	10
4	AlH_3	−78	direct	86	14
5	AlH_3	−78	inverse	88	12
6	DIBALH	−78	inverse	80	20

[a] Direct: addition of the hydride to a solution of **7** in THF. Inverse: addition of a solution of **7** in THF to the hydride.

ture and the order of addition of the reagents were shown to influence slightly the stereoselectivity of the process. The best result was achieved by addition of $LiAlH_4$ to a THF solution of ketone **7** at −100°C, which gave, in quantitative yield, a 93:7 mixture of (1*S*)-**19** and (1*R*)-**19**, which was used without further purification in the next step. Neither AlH_3 nor DIBALH were able to increase the diastereoselectivity of this reduction. Other reagents which were checked in order to explore the possibility of forming the epimer (1*R*)-**19** as a major component were fruitless. Bulky hydrides, such as L-Selectride or $LiBHEt_3$, as well as Luche reagent, afforded different mixtures of 1,2- and 1,4-hydride addition products being always (1*S*)-**19** the major component of the final mixtures. The (*S*) absolute configuration at C-1 of **19** as well as its enantiomeric excess (*ee* >97%) were determined after formation of the corresponding Mosher's esters.[28] Finally, protection of **19** as the isobutyrate ester **20**

(79% yield for the two last steps) and Stille coupling reaction with tributylvinylstannane (78% yield) gave rise to vinylcyclohexene **4** bearing the three stereogenic centers present in the natural angucyclinones, with the appropriate absolute configuration (Scheme 4).

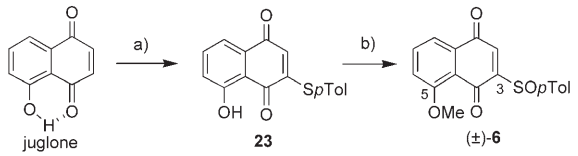
With the enantiopure diene in hand, the completion of the angucyclinones syntheses required the preparation of the dienophiles (±)-**5** and (±)-**6**. Racemic 5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**5**)[31] was prepared (Scheme 5) from 2-bromo-1,4,5-trimethoxy naphthalene



Scheme 5. Synthesis of (±)-5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**5**): a) *n*BuLi, THF, −78°C; then MeOSO*p*Tol, −78°C, 2 h, 65%; b) CAN, MeCN, H_2O, RT, 1 h, 79%.

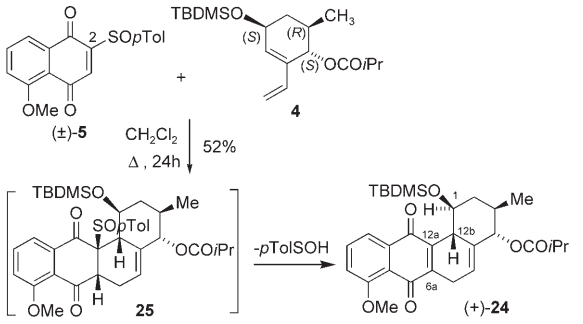
(**21**),[32] by lithium–bromine exchange followed by treatment with methyl *p*-toluene sulfinate.[33] Oxidation of the diaromatic sulfoxide **22** with cerium ammonium nitrate (CAN) occurred selectively at the more electron-rich dimethoxy substituted aromatic ring, giving rise to 2-(*p*-tolylsulfinyl) juglone methyl ether (**5**) in 79% yield (Scheme 5).

For the synthesis of racemic 3-(*p*-tolylsulfinyl)-substituted methyl juglone (**6**), we started from commercially available juglone which was known to react regioselectively with *p*-tolylthiophenol affording 3-(*p*-tolylthio)-1,4,5-trihydroxynaphthalene.[34] The product initially formed suffered a spontaneous air oxidation in the reaction medium, rendering 3-(*p*-tolylthio)juglone (**23**) in 67% yield. Quantitative formation of the methyl ether with methyl iodide in the presence of silver oxide[35] followed by thio ether controlled oxidation using *m*-CPBA at −78°C, afforded 3-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**6**) in 70% isolated yield (Scheme 6).



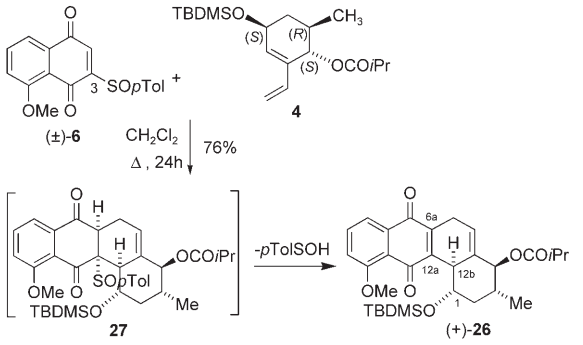
Scheme 6. Synthesis of (±)-5-methoxy-3-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**6**): a) *p*TolSH, EtOH, 0°C, 4 d, 67%; b) i) Ag_2O, MeI, CH_2Cl_2, RT, 2 d, 99%; ii) *m*-CPBA, CH_2Cl_2, −78°C, 4 h, 70%.

We then proceeded to the construction of the tetracyclic skeleton of derivatives **1**--**3** through the Diels–Alder reaction with enantiomerically pure vinyl cyclohexene **4**. After refluxing two equivalents of (±)-2-(*p*-tolylsulfinyl)-juglone methyl ether (**5**) with diene **4** in CH_2Cl_2 for 24 h, the tetracyclic quinone (+)-**24** was obtained as a sole regioisomer and pure diastereomer, in 52% yield. Compound **24** resulted from a regioselective Diels–Alder reaction, followed by the spontaneous elimination of *p*-tolylsulfenic acid, which regenerated the quinonic double bond (Scheme 7).



Scheme 7. Diels–Alder reaction between diene **4** and (±)-5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**5**).

Under similar conditions, (±)-5-methoxy-3-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**6**) reacted with **4** leading to the exclusive formation of tetracyclic quinone (+)-**26** in 76% yield (Scheme 8). Compound **26** also resulted from the spontane-



Scheme 8. Diels–Alder reaction between diene **4** and (±)-5-methoxy-3-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**6**).

ous elimination of the sulfoxide in the initially formed cycloadduct **27** (see Scheme 8), which was formed in a completely region- and diastereoselective way. The regiochemistry of the initial Diels–Alder adduct **27**, resulting from juglone methyl ether **6** bearing the sulfoxide at C-3, must be the opposite to that of adduct **25** formed from juglone derivative **5** with the sulfoxide at C-2.

Regio- and stereochemistry: The regiochemistry of Diels–Alder reactions with juglone derivatives and other substituted naphthoquinones is well known.[36] As shown in Figure 2, the presence of the intramolecularly associated OH in juglone increases the electron withdrawing character of the C-4 carbonyl polarizing the C_2=C_3 quinonic double bond. In Diels–Alder reactions with juglone methyl ether **28**, the main factor in the regiocontrol of cycloadditions with electron-rich dienes, is the electron donating effect of the 5-OMe substituent (Figure 2), which makes the C-4 carbonyl the less electron-withdrawing substituent on C_2=C_3 double

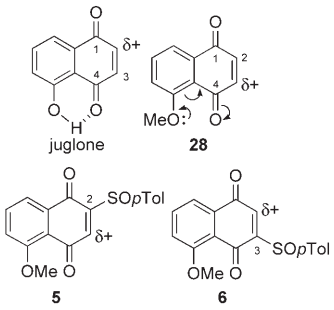


Figure 2. Expected polarization of differently substituted juglone derivatives.

bond. As a result, the value of the coefficient of the LUMO of the C-1 carbonyl remote from the OMe group become larger and the dienophilic double bond of **28** is polarized as shown.[36e] The presence of a sulfoxide at C-2 in juglone methyl ether derivative **5**, reinforces the polarization effect of the OCH_3 group and cooperates in the regiochemical control of Diels–Alder reactions.[12,17] Up to date, the effect of the sulfoxide at C-3 in juglone derivative **6**, was unknown. The structure of tetracyclic compound **24**, resulting from the reaction between diene **4** and sulfinyl quinone **5**, was a consequence of the initial formation of the not isolated *ortho*-adduct **25** (Scheme 7); its regiochemistry was as expected taking into account the 1,2-disubstitution of the butadiene derivative **4**[5e,f] and the above considerations on dienophile **5**. This is in sharp contrast to the moderate regioselectivitity reported for cycloadditions of 2-*p*-tolylsulfinyl juglone acetate.[36a]

Even more interesting was the opposite regiochemical control of the cycloaddition between 3-(*p*-tolyl)sulfinyl juglone methyl ether (**6**) and diene **4** which is exclusively dictated by the sulfoxide. This result showed that the effect of the sulfoxide in the regiochemical control is more powerful than that of the C-5 OMe substituent in the unsubstituted system **28**, giving rise to the formation of the regioisomeric *ortho*-adduct **27** upon reaction with chiral diene **4** (Scheme 8).

The absolute configurations of the new stereogenic centers created at C-12b in the domino Diels–Alder reaction/sulfoxide elimination process leading to **24** and **26** were established on the base of the known configurations of the stereogenic centers at the A ring as well as their ^{1}H NMR data. Double resonance experiments on **24** disclosed the existence of a doublet at δ 3.38 ppm showing a coupling constant of $J_{1,12b} = 9.4$ Hz, which was assigned to H_{12b} situated in a *trans*-diaxial disposition with respect to H-1.[37] We thus assigned the (*R*) absolute configuration to C-12b. This is in accordance with a process corresponding to the formation of the *ortho*-adduct in an *endo* fashion, *anti* with respect to the OTBDMS substituent of the vinyl cyclohexene.

The π-facial approach on both diene and dienophile was dictating the stereochemistry at C-12b, which must result from a double asymmetric induction process. Precedent work by Frank[38] and Larsen[39] had shown that the stereochemical course of Diels–Alder reactions with chiral vinylcyclohexenes bearing an allylic oxygenated substituent at C-3 was governed also by steric factors involving the size of the allylic substituents. As shown in Figure 3 (**A**[38] and **B**[39])

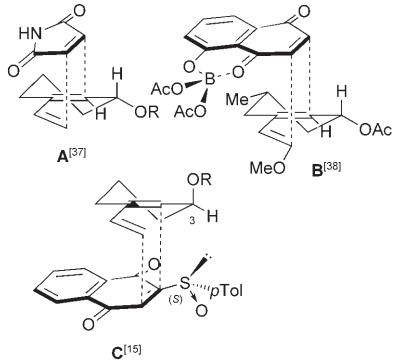


Figure 3. Favored approaches of chiral semicyclic dienes in Diels–Alder reactions with different dienophiles.

the models proposed by these authors to justify the major or exclusive formation of the *anti* cycloadducts, corresponded to the preferred *endo* approach of the dienophile from the face of the diene *anti* to the oxygenated function.

With respect to the π-diastereofacial selectivity of Diels–Alder reactions of enantiopure 2-(*p*-tolylsulfinyl)quinones with simple dienes, our previous results had suggested that the most favored *endo* approach of the diene normally occurred from the face of the sulfinyl quinone containing the less sterically demanding lone electron pair of the sulfoxide on the reactive s-*cis* conformation.[13] When the diene partner was a chiral C-3 oxygenated vinylcyclohexene (**C** in Figure 3), the stereochemical course of the cycloaddition with enantiopure (S*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone was a consequence of the preference for the *anti* approach of the diene, to the less hindered upper face of the s-*cis* conformation of the quinone.[15]

On the basis of the above-mentioned model of approach and the experimental data, we propose that diastereomers **24** and **26**, resulting from reaction between enantiopure diene **4** and racemic **5** or **6**, must arise from transition state *endo-anti*-**TSI**, shown in Figure 4. A double asymmetric induction process, where the matched pair in the cycloaddition corresponded to the (*R*) enantiomer of the sulfinyl-dienophile **5** or **6** reacting with the enantiopure diene (3*S*,5*R*,4*S*)-**4** (**TSI**, Figure 4). This was supported by the need of double molar amount of quinones **5** or **6** versus **4**, to achieve completion of the reaction in 24 h (see Experimental Section). The OTBDMS group at C-3 must be the responsible of the facial diastereoselectivity observed, directing the diene approach *anti* to the bulkier allylic C-3 OTBDMS substituent leading to the C-12b (*R*) absolute configuration. As can be seen in **TSI**, the C-3 allylic group is proximal to the sulfoxide in this *endo* approach. Thus, more severe interactions would appear between the bulky OTBDMS substituent and the sulfoxide group if the *syn-endo* attack would take place.

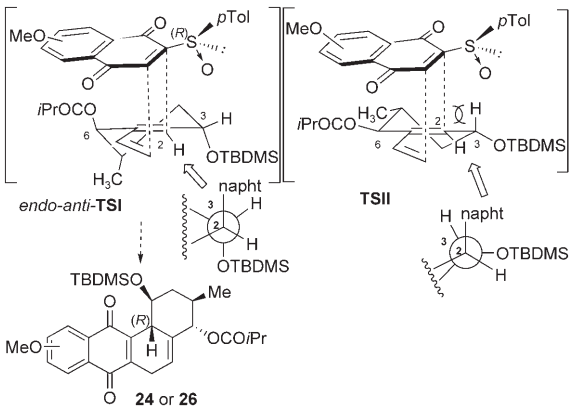


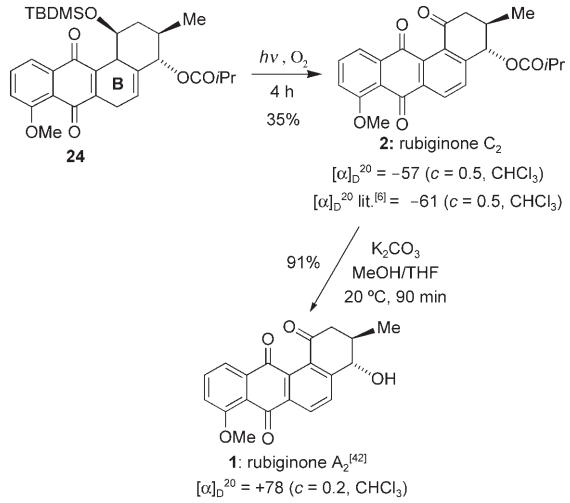
Figure 4. Favored approach of enantiopure vinylcyclohexene **4** in Diels–Alder reactions with sulfinyl naphthoquinones **5** or **6**.

Due to this closer disposition, the stereochemical course with dienophiles **5** or **6** must be identical, independently of the location of the OMe group on the naphthyl moiety.

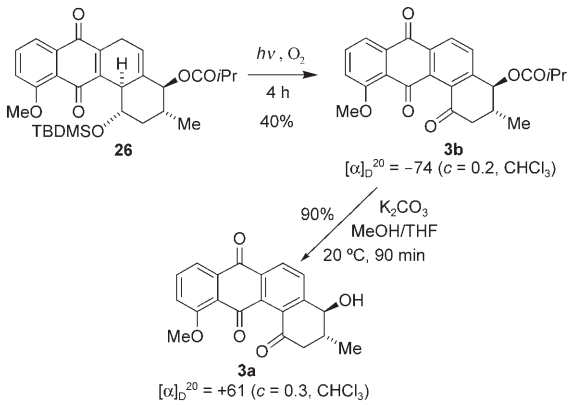
An interesting aspect of the stereochemical model labelled *endo-anti*-**TSI** that should be mentioned, is the proposed chair-like conformation of the reacting vinylcyclohexene **4**. Two possible conformations could result from the *anti* approach represented as **TSI** and **TSII** in Figure 4. Both would evolve into **25** or **27** initial adducts, but according to Houk's work,[40] allylic substituents on the diene moiety must be staggered with respect to the forming bonds in the transition state to avoid torsional strain. The torsional interaction existent in **TSII** between the partially formed C–C bond and the pseudoaxial C_3-H allylic is highly destabilizing. The transition state **TSI** would eventually alleviate this torsional strain leading to a more stable situation.

Next step in the transformation of **24** and **26** towards rubiginones **1** and **2** and their regioisomers **3a** and **3b** was the controlled aromatization of the B ring. All the experiments carried out under the standard aromatization conditions (DBU, DDQ or K_2CO_3), gave complex reaction mixtures where the desired products were even not detected. In several experiments, we observed that adducts **24** and **26** were extremely sensitive to light and evolved, in the presence of air, into different mixtures of products, where final rubiginones could be detected. Finally, we could establish that upon exposure of **24** to sunlight in the presence of air under solvent-free conditions,[41] a slow evolution occurred to give rubiginone C_2 (**2**) which was isolated pure by column chromatography in 35% yield (Scheme 9). Synthetic **2** was identical in all physical and spectroscopic data to natural (−)-rubiginone C_2 (**2**).[6] The other natural product, (+)-rubiginone A_2 (**1**), was obtained by methanolysis of (−)-**2** with K_2CO_3/MeOH/THF, affording, in 91% yield, compound **1** {$[\alpha]_D^{20} = +78$ ($c = 0.2$ in $CHCl_3$)}, identical in all aspects to natural (+)-rubiginone A_2.[42]

Regioisomeric derivative **26** showed a similar behavior, and, upon sunlight irradiation in the presence of air under solvent-free conditions evolved into tetracyclic quinone **3b** {$[\alpha]_D^{20} = -74$ ($c = 0.2$ in $CHCl_3$)}—a regioisomer of the natural rubiginone C_2 (**2**)—that was isolated pure in 40% yield (Scheme 10). Methanolysis of the isobutyric ester at C-4 with K_2CO_3/MeOH/THF afforded carbinol **3a** {$[\alpha]_D^{20} = +61$ ($c = 0.3$ in $CHCl_3$)}, which is a regioisomer of natural rubiginone A_2 (**1**), in 90% yield.



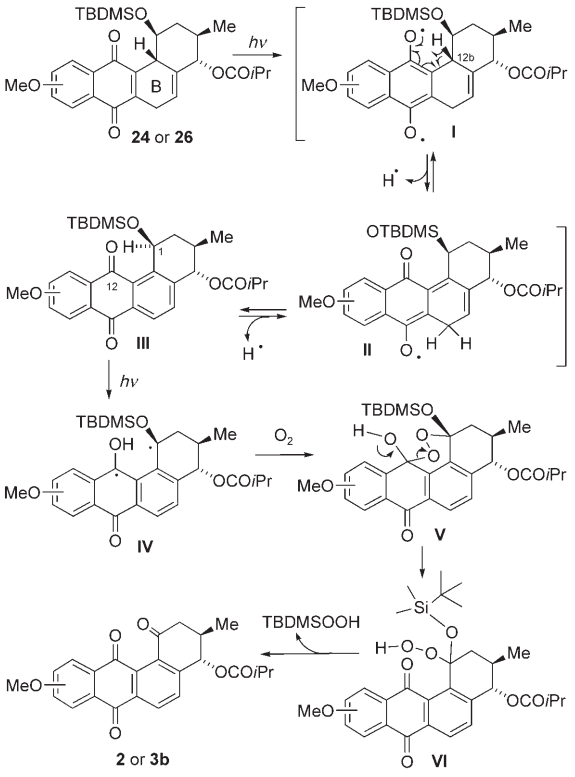
Scheme 9. Synthesis of rubiginones C_2 (**2**) and A_2 (**1**) from tetracyclic precursor **24**.



Scheme 10. Synthesis of regioisomeric angucyclinones **3a** and **3b** from tetracyclic precursor **26**.

This unprecedented photoinduced one-pot transformation implied a domino sequence of three reactions on **24** and **26** in a very efficient way: aromatization of the B ring, deprotection of the silyl ether and oxidation of the C-1 position into a carbonyl group. Although the relative order of these reactions has not been unequivocally established, according to previous observations of photoinduced oxidations of angucyclinone systems,[10] we propose the mechanism depicted in Scheme 11 for this domino process.

We assume that the aromatization of the B ring of **24** or **26** had to occur first to facilitate further transformations. The photo-aromatization may take place through the intermediate formation of an excited state oxygen centered biradical **I**,[43] from the naphthoquinone moiety of **24** or **26**, fol-



Scheme 11. Proposed mechanism for the sunlight-mediated transformation of **24** or **26** into angucyclinones **2** and **3b**.

lowed by elimination of a hydrogen radical from the angular C-12b benzylic carbon, leading to **II**. A second hydrogen radical elimination from **II** could occur to give the angularly fused anthraquinone system **III**. As proposed by Krohn[44] in analoguous systems, an intramolecular hydrogen transfer from the C-1 situated in the γ-position with respect to the C-12 carbonyl in **III** in a Norrish type II process would produce a new 1,4-biradical **IV**. This process must be easy due to the adequate geometric disposition of both the C–H bond at C-1 and the carbonyl group at C-12.[45] The subsequent reaction of **IV** with singlet oxygen must take place through the intermediate formation of a peroxy radical,[46] to give the cyclic peroxide **V**. Although some cyclic peroxide hemiketals are stable compounds[47] we did not detect compound **V**, which evolved directly into the rubiginone C_2 (**2**) or the regioisomer **3b**. The driving force of the rapid transformation of **V** into **VI**, must be the formation of the highly stable conjugate quinone system. Photochemical cleavage of silanes and polysilanes has been reported to occur when close oxygen functionalities can assist the reaction.[48] In our case, the deprotection of the silyloxy hydroperoxy group in **VI**, can take place easily with assistance of the hydroperoxy moiety whose instability as a hydroperoxy silyl hemiketal must favor a rapid reaction leading to the conjugate ketone of the final products **2** and **3a**.

Conclusion

In summary, we have reported the total enantioselective synthesis of the C-4 oxygenated angucyclinones rubiginones A_2 (**1**), C_2 (**2**) and their C-11 methoxy regioisomers **3a** and **3b**, based on the asymmetric Diels–Alder reaction between the enantiopure vinyl cyclohexene (+)-**4** and the racemic methoxy substituted sulfinylnaphthoquinones **5** and **6**. The successful route presented employed the chemo- and stereoselective addition of Me_3Al to (S*S*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinol (**9**) and the elimination of the chiral sulfoxide as methyl *p*-tolylsulfone in the intermediate β-hydroxy sulfone **8**, as the key steps for the synthesis of enantiopure diene **4**. Compound **4** was thus obtained in nine steps and 26% overall yield from **9**. The regioselective construction of the tetracyclic skeleton of natural angucyclinones (+)-**1**, (−)-**2** and the C-11 methoxy regioisomers (−)-**3a** and (−)-**3b** was achieved in a stereocontrolled Diels–Alder reaction between **4** and the C-2 or C-3 sulfoxide-bearing juglone derivatives **5** and **6**, after a domino cycloaddition/sulfoxide elimination process. The inversion of the regioselectivity observed in the cycloadditions of **5** and **6**, showed the efficiency of the sulfoxide in the regiochemical control, being remarkable in the case of **6**, where the regiochemistry was the opposite to that expected with 5-methoxy-1,4-naphthoquinone lacking the sulfoxide. Another noteworthy feature of our synthesis was the practical domino light-induced sequence involving B ring aromatization, OTBDMS deprotection and oxidation at C-1 of derivatives **24** and **26** allowing the total enantioselective synthesis to occur in 11 steps from *p*-quinol **9** with >98% *ee* and 4.4, 4.8, 6.5 and 7.2% overall yield, for rubiginones A_2 (**1**), C_2 (**2**) and their regioisomers **3a** and **3b**, respectively.

Experimental Section

General: Melting points were obtained in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Diastereoisomeric ratios were established by integration of well-separated signals of both diastereomers in the crude reactions mixtures. All reactions were monitored by thin-layer chromatography that was performed on precoated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230–400 mesh) of Merck. Eluting solvents are indicated below. The apparatus for inert atmosphere experiments was flame-dried under a stream of dry argon. THF and CH_2Cl_2 were dried over 4 Å molecular sieves. Diisopropylamine was distilled from KOH. All other reagent quality solvents were used without purification. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2, and solvent drying with $MgSO_4$.

(S*S*)-4-Hydroxy-4-[(*p*-tolylsulfinyl)methyl]-cyclohexa-2,5-dienone (9): *n*BuLi 2.4 M in hexanes (56 mL, 135.5 mmol) was added under argon at −78 °C to a solution of freshly distilled diisopropylamine (20.7 mL, 147.8 mmol) in THF (250 mL). After stirring for 30 min, a solution of (S*S*)-methyl-*p*-tolylsulfoxide (**12**)[26] (19.0 g, 123.2 mmol) in THF (200 mL) was added at −78 °C. After 30 min, a solution of 4,4-dimethoxy-2,5-cyclohexadienone (**11**)[24] (19.9 g, 129.4 mmol) in THF (430 mL) was slowly added and the mixture was stirred for 2 h at −78 °C. The mixture was hydrolyzed with an aqueous saturated solution of ammonium chloride (40 mL) and the organic layer was extracted with EtOAc. After workup, the crude product was dissolved in THF (80 mL) and a solution

of oxalic acid (1.16 g, 12.9 mmol) in water (20 mL) was added. After stirring for 2 h, hydrolysis with saturated solution of $NaHCO_3$, extraction with EtOAc and workup, the residue was recrystallized from EtOAc/hexane giving compound **9** as a white solid (24.5 g, 76%). M.p. 142–144 °C; $[\alpha]_D^{20}=-177$ ($c=1$ in $CHCl_3$); ^{1}H NMR: $\delta=7.54$, 7.36 (AA′BB′ system, 4H), 7.25 (dd, $J=10.2$, 3.2 Hz, 1H), 7.00 (dd, $J=10.2$, 3.2 Hz, 1H), 6.30 (dd, $J=10.2$, 1.8 Hz, 1H), 6.18 (dd, $J=10.1$, 1.9 Hz, 1H), 4.93 (s, 1H), 3.16, 2.85 (AB system, $J=13.3$ Hz, 2H), 2.43 (s, 3H); ^{13}C NMR: $\delta=184.9$, 149.2, 149.1, 142.2, 139.6, 130.1 (2C), 128.1, 127.6, 123.9 (2C), 68.0, 67.1, 21.3; elemental analysis calcd (%) for $C_{14}H_{14}O_3S$ (262.3): C 64.10, H 5.38, S 12.22; found C 63.91, H 5.48, S 12.47.

[4*R*,5*R*,*SS*]-4-Hydroxy-5-methyl-4-[(*p*-tolylsulfinyl)methyl]-2-cyclohexen-1-one (13): A solution of **9** (500 mg, 1.9 mmol) in CH_2Cl_2 (10 mL) was added under argon at −78 °C to a solution of Me_3Al 2 M in heptane (3.8 mL, 7.6 mmol) in CH_2Cl_2 (10 mL). After 4 h at the same temperature, the excess of Me_3Al was destroyed with methanol, and the mixture was poured into an Erlenmeyer containing EtOAc and a saturated solution of sodium potassium tartrate and stirred vigorously for 30 min. The organic layer was washed with brine and dried over $MgSO_4$. After workup and flash chromatography (EtOAc/hexane 1:1), compound **13** was obtained as a white solid (345 mg, 65%). M.p. 120–121 °C (EtOAc/hexane); $[\alpha]_D^{20}=-245$ ($c=1$ in $CHCl_3$); ^{1}H NMR: $\delta=7.56$, 7.37 (AA′BB′ system, 4H), 7.25 (d, $J=10.2$ Hz, 1H), 6.10 (dd, $J=10.2$ Hz, 1H), 4.85 (s, 1H), 3.22, 2.92 (AB system, $J=12.2$ Hz, 2H), 2.62–2.22 (m, 3H), 2.44 (s, 3H), 1.10 (d, $J=7.0$ Hz, 3H); ^{13}C NMR: $\delta=198.3$, 149.7, 142.4, 139.7, 130.3 (2C), 129.0, 123.8 (2C), 71.6, 64.9, 41.7, 38.8, 21.3, 14.2; elemental analysis calcd (%) for $C_{15}H_{18}O_3S$ (278.4): C 64.72, H 6.52, S 11.52; found C 64.69, H 6.85, S 11.89.

(4*R*,5*R*)-4-Hydroxy-5-methyl-4-[(*p*-tolylsulfonyl)methyl]-2-cyclohexen-1-one (15): A solution of *m*-CPBA (6.2 g, 17.9 mmol) in CH_2Cl_2 (60 mL) was added dropwise at 0 °C to a solution of **13** (3.8 g, 13.8 mmol) in CH_2Cl_2 (45 mL). After stirring at 0 °C for 30 min, the mixture was hydrolyzed with an aqueous saturated solution of Na_2SO_3, extracted with CH_2Cl_2, and the organic layer washed with an aqueous saturated solution of $NaHCO_3$. After workup and recrystallization (EtOAc/hexane), compound **15** was obtained as a white solid (3.9 g, 96%). M.p. 145–146 °C; $[\alpha]_D^{20}=-65$ ($c=1$ in acetone); ^{1}H NMR: $\delta=7.80$, 7.39 (AA′BB′ system, 4H), 7.05 (dd, $J=10.2$, 0.9 Hz, 1H), 5.95 (d, $J=10.2$ Hz, 1H), 4.08 (br s, 1H), 3.50, 3.45 (AB system, $J=14.2$ Hz, 2H), 2.62–2.37 (m, 3H), 2.47 (s, 3H), 1.09 (d, $J=6.6$ Hz, 3H); ^{13}C NMR: $\delta=198.3$, 149.7, 142.4, 139.9, 130.2 (2C), 129.1, 123.8 (2C), 71.7, 64.9, 41.7, 38.9, 21.4, 14.3; elemental analysis calcd (%) for $C_{15}H_{18}O_4S$ (294.4): C 61.20, H 6.16, S 10.89; found C 61.12, H 6.19, S 11.24.

(1*R*,4*S*,6*R*)-6-Methyl-1-[(*p*-tolylsulfonyl)methyl]-2-cyclohexen-1,4-diol (16): A solution of **15** (3.9 g, 13.3 mmol) in THF (45 mL) was added dropwise under argon at −78 °C to a solution of DIBALH 1 M in hexanes (39.8 mL, 39.8 mmol) in THF (130 mL). After 30 min at the same temperature, the excess of DIBALH was destroyed with methanol, and the mixture was poured into an Erlenmeyer containing ethyl acetate and a saturated solution of sodium potassium tartrate and stirred vigorously for 30 min. The organic layer was washed with brine and dried over $MgSO_4$. After workup, compound **16** was obtained as a white solid (3.7 g, 99%), which could be used in the next step without further purification. M.p. 96–97 °C (EtOAc/hexane); $[\alpha]_D^{20}=-56$ ($c=1$ in acetone); ^{1}H NMR: $\delta=$ 7.79, 7.36 (AA′BB′ system, 4H), 6.17 (dd, $J=10.1$, 2.0 Hz, 1H), 5.85 (dt, $J=10.1$, 1.8 Hz, 1H), 4.5 (s, 1H), 4.23 (m, 1H), 3.46, 3.25 (AB system, $J=14.3$ Hz, 2H), 2.46 (s, 3H), 1.85 (m, 2H), 1.68–1.51 (m, 2H), 1.01 (d, $J=6.7$ Hz, 3H); ^{13}C NMR: $\delta=$ 144.9, 138.2, 134.6, 130.0, 129.9 (2C), 127.7 (2C), 70.3, 67.2, 63.3, 36.1 (2C), 21.6, 14.9; elemental analysis calcd (%) for $C_{15}H_{20}O_4S$ (296.1): C 60.79, H 6.80, S 10.82; found C 60.46, H 7.14, S 10.56.

(1*R*,4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy)]-6-methyl-1-[(*p*-tolylsulfonyl)methyl]-2-cyclohexen-1-ol (8): 2,6-Lutidine (1.8 mL, 14.9 mmol) and TBDMSOTf (1.8 mL, 25.3 mmol) were added at 0 °C under argon to a solution of **16** (1.8 g, 6.0 mmol) in dry CH_2Cl_2 (20 mL). After 2 h, the mixture was hydrolyzed with 10% HCl, extracted with CH_2Cl_2 and the organic layer washed with brine. After workup, compound **8** was obtained as a yellowish oil (2.2 g, 93%), which could be use in the next step without further purification. An analytical sample was obtained after flash chromatography (EtOAc/hexane 1:3) and recrystallization in ethyl ether/hexane, giving **8** as a white solid (200 mg). M.p. 107–108 °C; $[\alpha]_D^{20}=+41$ ($c=1$ in acetone); ^{1}H NMR: $\delta=7.78$, 7.36 (AA′BB′ system, 4H), 6.04 (dd, $J=10.1$, 2.0 Hz, 1H), 5.76 (dt, $J=10.1$, 2.0 Hz, 1H), 4.23 (m, 1H), 3.44, 3.29 (AB system, $J=14.2$ Hz, 2H), 2.59 (s, 1H), 2.45 (s, 3H), 1.91 (m, 1H), 1.74–1.53 (m, 2H), 1.01 (d, $J=6.9$ Hz, 3H), 0.89 (s, 9H), 0.08, 0.07 (2s, 6H); ^{13}C NMR: $\delta=$ 144.8, 138.1, 135.9, 129.9 (2C), 129.8, 127.7 (2C), 70.3, 67.7, 63.2, 36.4, 35.7, 25.8 (3C), 21.6, 18.1, 15.0, −3.6, −3.7; FAB MS: *m*/*z*: calcd for $C_{21}H_{34}OSSi$: 411.1947, found 411.2026 $[M+H]^+$; FAB MS: *m*/*z* (%): 411 (7) $[M+H]^+$, 393 (100), 371 (46).

(4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-one (17): Cs_2CO_3 (3.9 g, 12 mmol) was added to a solution of **8** in CH_3CN (60 mL). After stirring for 17 h, the reaction mixture was hydrolyzed with water and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. After workup and purification by flash chromatography (EtOAc/hexane 1:12), compound **17** was obtained as a colorless oil (1.25 g, 87%) for the final two steps. $[\alpha]_D^{20}=-76$ ($c=1$ in acetone); ^{1}H NMR: $\delta=6.77$ (dt, $J=10.1$, 2.0 Hz, 1H), 5.91 (dd, $J=10.1$, 2.4 Hz, 1H), 4.59 (m, 1H), 2.38 (m, 1H), 2.20 (m, 1H), 1.77 (ddd, $J=$ 13.9, 12.5, 10.3 Hz, 1H), 1.14 (d, $J=6.5$ Hz, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR: $\delta=$ 201.0, 154.0, 128.2, 68.0, 41.9, 40.1, 25.7 (3C), 18.0, 15.0, −3.5, −3.7; EI MS: *m*/*z*: calcd for $C_9H_{15}O_2Si$: 183.0841; found: 183.0846 $[M-C_4H_9]^+$; EI MS: *m*/*z* (%): 183 (100) $[M-C_4H_9]^+$, 139 (10), 113 (15).

(4*S*,6*R*)-2-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-one (7): A solution of bromine (15 μL, 0.30 mmol) in CCl_4 (3 mL) was added dropwise at 0 °C to a solution of **17** (72 mg, 0.30 mmol) in CCl_4 (3 mL). When no starting material was observed, triethylamine (0.15 mL, 1.1 mmol) was added and the mixture was stirred at RT for 32 h. The reaction mixture was quenched with aqueous saturated solution of Na_2SO_3 and extracted with CH_2Cl_2. After workup and flash chromatography (EtOAc/hexane 1:120), compound **7** was obtained as a white solid (77 mg, 80%). M.p. 40–41 °C; $[\alpha]_D^{20}=-38$ ($c=1$ in acetone); ^{1}H NMR: $\delta=7.22$ (m, 1H), 4.59 (m, 1H), 2.46 (m, 1H), 2.25 (m, 1H), 1.87 (m, 1H), 1.21 (d, $J=6.7$ Hz, 3H), 0.91 (s, 9H), 0.13, 0.12 (2s, 6H); ^{13}C NMR: $\delta=193.1$, 154.3, 123.4, 69.0, 41.6, 40.0, 25.7 (3C), 18.0, 15.6, −3.4, −3.6; elemental analysis calcd (%) for $C_{13}H_{23}BrO_2Si$ (319.3): C 48.90, H 7.26; found C 48.88, H 7.56.

(4*S*,6*S*)-2,6-Dibromo-4-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-one (18): When the above mentioned reaction was performed with an excess of bromine, compound **18** was obtained as a yellow oil. $[\alpha]_D^{20}=-29$ ($c=1.9$ in acetone); ^{1}H NMR: $\delta=7.16$ (dd, $J=2.3$, 2.2 Hz, 1H), 4.64 (ddd, $J=7.2$, 5.0, 2.2 Hz, 1H), 2.56 (ddd, $J=14.4$, 5.0, 2.1 Hz, 1H), 2.07 (dd, $J=14.4$, 9.1 Hz, 1H), 1.88 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR: $\delta=$ 184.6, 153.9, 120.0, 68.4, 58.2, 48.9, 28.5, 25.7, 18.0, −3.4, −3.5; EI MS: *m*/*z*: calcd for $C_{13}H_{22}Br_2O_2Si$: 395.9756; found: 395.9754 $[M]^+$.

(1*S*,4*S*,6*R*)-2-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-ol (19): A solution of $LiAlH_4$ (31 mg, 0.76 mmol) in THF (25 mL) was added under argon to a solution of **7** (163 mg, 0.51 mmol) in THF (17 mL) at −100 °C. After 30 min at the same temperature, the reaction was hydrolyzed with methanol, and the mixture was poured into an Erlenmeyer flask containing ethyl acetate and a saturated solution of sodium potassium tartrate and stirred vigorously for 30 min. The organic layer was washed with brine and dried over $MgSO_4$. After workup, compound **19** was isolated, in quantitative yield, as a 93:7 diastereoisomeric mixture, which was used without further purification in the next step. An analytical sample of **19** could be isolated pure by HPTLC as a white solid. M.p. 88–89 °C; $[\alpha]_D^{20}=-67$ ($c=1$ in $CHCl_3$); ^{1}H NMR: $\delta=6.05$ (d, $J=1.6$ Hz, 1H), 4.29 (m, 1H), 3.82 (m, 1H), 2.24 (d, $J=3.6$ Hz, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.45 (m, 1H), 1.15 (d, $J=6.5$ Hz, 3H), 0.89 (s, 9H), 0.08, 0.07 (2s, 6H); ^{13}C NMR: $\delta=136.4$, 128.4, 75.8, 68.9, 39.9, 36.3, 25.8 (3C), 19.0, 18.1, −3.5, −3.6; elemental analysis calcd (%) for $C_{13}H_{25}BrO_2Si$ (321.33): C 48.59, H 7.84; found C 48.33, H 7.54.

(1*S*,4*S*,6*R*)-2-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-2-cyclohexen-1-yl isobutyrate (20): Isobutyryl chloride (76 μL, 0.71 mmol) and 4-dimethylaminopyridine (135 mg, 1.1 mmol) were added to a solution of the

above obtained mixture containing **19** dissolved in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 1 h, hydrolyzed with water and extracted with CH_2Cl_2. After workup and flash chromatography (EtOAc/hexane 1:50), isobutyrate ester **20** was obtained as a colorless oil (158 mg, 79% yield over two steps). ^{1}H NMR: δ=6.14 (dd, J=3.6, 1.6 Hz, 1H), 5.32 (m, 1H), 4.32 (m, 1H), 2.61 (sept, J=7.1 Hz, 1H), 1.92 (m, 2H), 1.52 (m, 1H), 1.21 (d, J=6.9 Hz, 3H), 1.20 (d, J=7.1 Hz, 3H), 0.99 (d, J=6.5 Hz, 3H), 0.88 (s, 9H), 0.07, 0.06 (2s, 6H); ^{13}C NMR: δ=176.4, 138.1, 122.9, 75.6, 68.5, 39.5, 34.9, 34.2, 25.7 (3C), 19.1, 19.0, 18.5, 18.0, −3.5, −3.6; EI MS: m/z: calcd for $C_9H_{13}BrO_3Si$: 333.0522; found: 333.0519 $[M-C_4H_9]^+$; EI MS: m/z (%): 333 (35) $[M-C_4H_9]^+$, 311 (71), 289 (14), 259 (9), 241 (100), 223 (15).

(1*S*,4*S*,6*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-2-vinyl-2-cyclohexen-1-yl isobutyrate (4): A mixture of compound **20** (583 mg, 1.5 mmol), tetrakistriphenylphosphine palladium (0) (207 mg, 0.18 mmol) and tributylvinylstannane (0.58 mL, 0.18 mmol) in toluene (7.5 mL) was heated at 90°C for 24 h. The reaction was hydrolyzed with water and extracted with CH_2Cl_2. After workup and flash chromatography (EtOAc/hexane 1:60), compound **2** was obtained as a colorless oil (393 mg, 78%). ^{1}H NMR: δ=6.13 (dd, J=17.8, 10.9 Hz, 1H), 5.84 (m, 1H), 5.46 (m, 1H), 5.13 (d, J=17.8 Hz, 1H), 4.99 (d, J=10.9 Hz, 1H), 4.45 (m, 1H), 2.51 (sept, J=6.9 Hz, 1H), 1.90 (m, 2H), 1.45 (m, 1H), 1.14 (d, J=6.9 Hz, 3H), 1.12 (d, J=6.9 Hz, 3H), 1.01 (d, J=6.9 Hz, 3H), 0.89 (s, 9H), 0.08, 0.07 (s, 3H); ^{13}C NMR: δ=177.0, 135.8, 135.7, 135.0, 114.2, 72.7, 66.9, 38.3, 34.2, 33.7, 25.8, 19.0, 18.9, 18.4, 18.1, −3.5, −3.6; FAB MS: m/z: calcd for $C_{15}H_{27}OSi$: 251.1831; found: 251.1829 $[M-C_4H_7O_2]^+$; FAB MS: m/z (%): 265 (9) $[M-C_3H_5O_2]^+$, 251 (100) $[M-C_4H_7O_2]^+$, 235 (52), 227 (10), 219 (37), 207 (22).

5-Hydroxy-3-(*p*-tolylthio)-1,4-naphthoquinone (23): A solution of *p*-tolylthiophenol (766 mg, 6.17 mmol) in EtOH (40 mL) was added dropwise to a solution of commercially available juglone (1.08 g, 6.17 mmol) in EtOH (40 mL) at 0°C. After 4 d, the precipitate was filtered and washed with cold EtOH, giving pure **23** as a red solid (1.23 mg, 67%). M.p. 168–169°C (lit.:[34] m.p. 171°C); ^{1}H NMR: δ=11.73 (s, 1H), 7.67–7.20 (m, 7H), 6.07 (s, 1H), 2.43 (s, 3H); ^{13}C NMR: δ=187.2, 181.2, 161.8, 156.7, 141.2, 137.0, 135.6 (2C), 132.2, 131.3, 131.2 (2C), 128.8, 123.7, 123.2, 119.3, 21.4.

5-Methoxy-3-(*p*-tolylsulfinyl)-1,4-naphthoquinone (6): Ag_2O (1.06 g, 4.57 mmol) and MeI (0.57 mL, 9.13 mmol) were added to a solution of **23** (1.23 g, 4.15 mmol) in CH_2Cl_2 (50 mL) in absence of light. After 2 d, the reaction mixture was filtered over Celite and the solvent removed under reduce pressure, to give 5-methoxy-3-(*p*-tolylthio)-1,4-naphthoquinone as a red solid (1.27 mg, 99%). M.p. 154–155°C; (lit.:[49] m.p. 154–155°C); ^{1}H NMR: δ=7.66–7.57 (m, 2H), 7.40–7.35 (m, 2H), 7.28–7.23 (m, 3H),6.00 (s, 1H), 3.99 (s, 3H), 2.39 (s, 3H); ^{13}C NMR: δ=181.9, 181.1, 160.1, 159.6, 140.7, 135.5 (2C), 135.4, 134.5, 131.0 (2C), 126.2, 124.3, 119.3, 119.2, 117.2, 56.4, 21.3.

A solution of *m*-CPBA (595 mg, 2.65 mmol) in CH_2Cl_2 (40 mL) was added dropwise at −78°C to a solution of 5-methoxy-3-(*p*-tolylthio)-1,4-naphthoquinone (791 mg, 2.55 mmol) in CH_2Cl_2 (40 mL). After 4 h, the reaction mixture was quenched with aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. After workup and recrystallization (EtOAc) compound **6** was obtained as a yellow solid (587 mg, 70%).[31] ^{1}H NMR: δ = 7.76–7.64 (m, 4H), 7.55 (s, 1H), 7.29–7.22 (m, 3H), 7.34 (s, 3H), 2.34 (s, 3H); ^{13}C NMR: δ = 183.0, 180.7, 160.2, 159.0, 142.5, 139.5, 135.9, 134.3, 131.9, 130.1 (2C), 126.0 (2C), 119.7, 118.2, 56.5, 21.5.

(1*S*,3*R*,4*S*,12b*R*)-1-[(*tert*-Butyldimethylsilyl)oxy)]-8-methoxy-3-methyl-7,12-dioxo-1,2,3,4,6,12b-hexahydrobenz[*a*]anthracen-4-yl isobutyrate (24): A solution of 5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (**5**)[31] (37 mg, 0.12 mmol) and diene **4** (16 mg, 0.048 mmol) in dry CH_2Cl_2 (1 mL) was heated under reflux for 24 h, under argon. After elimination of the solvent and flash chromatography (EtOAc/hexane 1:9), compound **24** was obtained as a yellowish solid (13 mg, 52%). M.p. 88–89°C; $[\alpha]_D^{20}$=−85 (c=0.25 in $CHCl_3$); ^{1}H NMR: δ=7.71 (dd, J=7.7, 1.4 Hz, 1H), 7.64 (t, J=7.9 Hz, 1H), 7.25 (dd, J=8.3, 1.4 Hz, 1H), 5.62–5.58 (m, 1H), 4.91–4.84 (m, 1H), 4.01 (s, 3H), 3.81 (m, 1H), 3.49 (ddt, J=24.7, 4.0, 2.2 Hz, 1H), 3.38 (m, 1H), 3.05 (ddt, J=24.5, 4.6, 2.2 Hz, 1H), 2.68 (sept, J=6.9 Hz, 1H), 1.97 (dd, J=8.9, 3.8 Hz, 1H), 1.69 (m, 2H), 1.26 (d, J=1.2 Hz, 3H), 1.23 (d, J=1.2 Hz, 3H), 1.01 (d, J=5.9 Hz, 3H), 0.73 (s, 9H), −0.12, −0.37 (2s, 6H); ^{13}C NMR: δ=183.7, 183.6, 176.1, 159.3, 142.9, 141.6, 135.2, 135.1, 134.5, 119.5, 116.9, 113.2, 77.3, 76.4, 56.4, 43.0, 42.9, 37.5, 34.3, 25.6 (3C), 25.1, 19.2, 19.1, 18.5, 17.8, −3.2, −3.3; EI MS: m/z: calcd for $C_{30}H_{40}O_6Si$: 524.2594; found: 524.2573 $[M]^+$; EI MS: m/z (%): 526 (62) $[M+2]^+$, 524 (54) $[M]^+$, 509 (57), 499 (41), 483 (100), 483 (100), 481 (71).

(1*S*,3*R*,4*S*,12b*S*)-1-[(*tert*-Butyldimethylsilyl)oxy)-11-methoxy-3-methyl-7,12-dioxo-1,2,3,4,6,7,12,12b-hexahydrobenz[*a*]anthracen-4-yl isobutyrate (26): A solution of 5-methoxy-3-(*p*-tolylsulfiny)-1,4-naphthoquinone (**6**) (89 mg, 0.29 mmol) and diene **4** (39 mg, 0.11 mmol) in dry CH_2Cl_2 (1 mL) was refluxed for 24 h, under argon. After elimination of the solvent and flash chromatography (EtOAc/hexane 1:9), compound **26** was obtained as a yellowish solid (44 mg, 76%). M.p. 102–103°C; $[\alpha]_D^{20}$=−149 (c=1 in $CHCl_3$); ^{1}H NMR: δ=7.71 (dd, J=7.7, 1.2 Hz, 1H), 7.61 (dd, J=8.3, 7.7 Hz, 1H), 7.23 (dd, J=8.3, 1.2 Hz, 1H), 5.61–5.57 (m, 1H), 4.90 (dd, J=10.1, 1.6 Hz, 1H), 3.95–3.88 (m, 4H), 3.50–3.35 (m, 2H), 3.10–2.96 (m, 1H), 2.68 (sept, J=6.9 Hz, 1H), 2.0–1.93 (m, 1H), 1.76–1.57 (m, 2H), 1.26 (d, J=1.8 Hz, 3H), 1.23 (d, J=1.6 Hz, 3H), 1.01 (d, J=6.1 Hz, 3H), 0.71 (s, 9H), −0.14 (s, 3H), −0.33 (s, 3H); ^{13}C NMR: δ=184.4, 182.7, 176.1, 158.9, 145.7, 138.5, 135.5, 134.1, 133.9, 120.8, 118.6, 117.2, 112.7, 77.2, 76.5, 55.9, 43.0, 42.9, 37.5, 34.2, 31.7, 29.2, 25.6 (3C), 24.6, 19.2, 19.1, 18.5, 17.8, −3.1, −3.3; EI MS: m/z: calcd for $C_{30}H_{40}O_6Si$: 524.2594; found 524.2572 $[M]^+$.

(3*R*,4*S*)-8-Methoxy-3-methyl-1,7,12(2*H*)-trioxo-3,4-dihydrobenz[*a*]anthracen-4-yl isobutyrate (2), rubiginone C_2: Compound **24** (42 mg, 0.08 mmol) was exposed, under solvent-free conditions, to the sunlight for 16 h. After flash chromatography (EtOAc/hexane 1:3) and recrystallization (EtOAc), compound **2** (rubiginone C_2) was obtained as a yellowish solid (11.5 mg, 35%). M.p. 218–219°C; $[\alpha]_D^{20}$=−57 (c=0.5 in $CHCl_3$); ^{1}H NMR: δ=8.35 (d, J=8.3 Hz, 1H), 7.78 (dd, J=7.7, 1.4 Hz, 1H), 7.72 (t, J=7.9 Hz, 1H), 7.59 (d, J=8.3 Hz, 1H), 7.31 (dd, J=8.1, 1.2 Hz, 1H), 5.84 (d, J=7.1 Hz, 1H), 4.04, (s, 3H), 3.17 (m, 1H), 2.75–2.56 (m, 3H), 1.24 (d, J=5.5 Hz, 3H), 1.22 (d, J=5.5 Hz, 3H), 1.12 (d, J=6.5 Hz, 3H); ^{13}C NMR: δ=196.6, 184.0, 181.2, 176.4, 159.9, 145.9, 137.5, 136.1, 135.5, 134.8, 134.6, 131.5, 130.1, 120.6, 119.7, 117.3, 73.3, 56.5, 43.8, 35.1, 34.1, 19.0, 18.9, 18.0; EI MS: m/z: calcd for $C_{24}H_{22}O_6$: 406.1416; found: 406.1421 $[M]^+$; EI MS: m/z (%): 406 (61) $[M]^+$, 336 (68), 318 (100), 294 (90), 151 (25), 71 (92).

[3*R*,r4*S*]-4-Hydroxy-8-methoxy-3-methyl-3,4-dihydrobenz[*a*]antracene-1,7,12(2*H*)-trione (1), rubiginone A_2: K_2CO_3 (10 mg, 72 μmol) was added to a solution of **2** (4 mg, 9.8 μmol) in methanol (0.5 mL) and THF (0.5 mL). After stirring for 90 min, the mixture was filtered through silica gel, and the solvent evaporated to give **1** (rubiginone A_2) as a yellowish solid (3.0 mg, 91%). M.p. (decomp) >215°C (EtOAc); $[\alpha]_D^{20}$=+78 (c=0.2 in $CHCl_3$); ^{1}H NMR: δ = 8.39, (d, J=8.3 Hz, 1H), 8.02 (dd, J=8.3, 1.0 Hz), 7.78 (dd, J=7.7, 1.4 Hz, 1H), 7.72 (t, J=7.9 Hz, 1H), 7.31 (dd, J=8.3, 1.4 Hz, 1H), 4.52 (m, 1H), 4.05 (s, 3H), 3.11 (dd, J=16.6, 5.7 Hz, 1H), 2.58 (dd, J=16.6, 10.7 Hz, 1H), 2.38 (m, 1H), 2.19 (d, J=6.9 Hz, 3H); ^{13}C NMR: δ=197.2, 184.3, 181.5, 159.9, 150.4, 137.5, 135.6, 135.5, 134.4, 134.0, 130.4, 130.2, 120.6, 119.7, 117.3, 73.5, 56.5, 44.8, 38.3, 18.2; EI MS: m/z: calcd for $C_{20}H_{17}O_5$: 337.1076: found 337.1069 $[M+H]^+$; EI MS: m/z (%): 337 (13) $[M+H]^+$, 307 (10).

(3*R*,4*S*)-11-Methoxy-3-methyl-1,7,12(2*H*)-trioxo-3,4-dihydrobenz[*a*]anthracen-4-yl isobutyrate (3b): Compound **26** (11.6 mg, 0.0221 mmol) was exposed, under solvent-free conditions, to the sunlight for 4 h. After flash chromatography (EtOAc/hexane 1:2) and recrystallization (EtOAc), compound **3** was obtained as a yellowish solid (3.6 mg, 40%). M.p. 165–166°C; $[\alpha]_D^{20}$=−74 (c=0.2 in $CHCl_3$); ^{1}H NMR: δ=8.28 (d, J=7.7 Hz, 1H), 7.82 (dt, J=7.7, 0.8 Hz, 1H), 7.68 (td, J=8.3, 0.6 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.31 (d, J=8.3 Hz, 1H), 5.86 (d, J=7.5 Hz, 1H), 4.02 (s, 3H), 3.21–3.12 (m, 1H), 2.72–2.60 (m, 3H), 1.24 (d, J=5.5 Hz, 3H), 1.22 (d, J=5.5 Hz, 3H), 1.12 (d, J=6.5 Hz, 3H); ^{13}C NMR: δ=196.6, 183.8, 182.4, 176.4, 159.1, 146.6, 138.8, 135.0, 134.8, 134.4, 133.7, 130.5, 129.4, 123.9, 119.3, 118.1, 73.4, 56.7, 43.6, 35.1, 34.1, 19.0, 18.9, 18.0; elemental analysis calcd (%) for $C_{24}H_{22}O_6$: C 70.92, H 5.46, found C 70.48, H 5.42.

[3*R*,4*S*]-4-Hydroxy-11-methoxy-3-methyl-3,4-dihydrobenz[*a*]antracene-1,7,12(2*H*)-trione (3a): K_2CO_3 (10 mg, 72 μmol) was added to a solution

of **3** (4 mg, 9.8 μmol) in methanol (0.5 mL) and THF (0.5 mL). After stirring for 90 min, the mixture was filtered through silica gel, and the solvent evaporated to give **3b** as a yellowish solid (3.0 mg, 91 %). M.p. (decomp) >215 °C (EtOAc); $[\alpha]_D^{20} = -62$ ($c = 0.2$ in $CHCl_3$); ^{1}H NMR: δ = 8.29, (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.2 Hz), 7.82 (d, J = 8.7 Hz, 1H), 7.66 (t, J = 8.8 Hz, 1H), 7.31 (d, J = 8.6 Hz, 1H), 4.54–4.49 (m, 1H), 4.02 (s, 3H), 3.09 (dd, J = 16.4, 5.1 Hz, 1H), 2.62–2.52 (m, 1H), 2.39–2.37 (m, 1H), 2.18 (d, J = 6.9 Hz, 3H); ^{13}C NMR: δ = 197.1, 184.1, 182.6, 159.0, 151.2, 138.5, 134.8, 134.3, 134.2, 133.2, 129.5, 129.4, 124.0, 119.2, 118.1, 73.6, 56.7, 44.6, 38.3, 18.2; FAB MS: calcd for $C_{20}H_{17}O_5$: 337.1084: found 337.1075 $[M+H]^+$; FAB MS: m/z (%): 337 (97), 154 (100), 136 (69).

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