Approaches to the stereocontrolled synthesis of anthracyclinones: preparation of optically pure bicyclic intermediates for the regioselective construction of the tetracyclic skeleton

José Luis García Ruano,* Cristina García Paredes, and José Alemán

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain
E-mail: joseluis.garcia.ruano@uam.es

Dedicated to Professor José Elguero on the occasion of his 70th birthday and Professor Pedro Molina on the occasion of his 60th birthday

(received 11 Jan 05; accepted 01 Apr 05; published on the web 08 Apr 05)

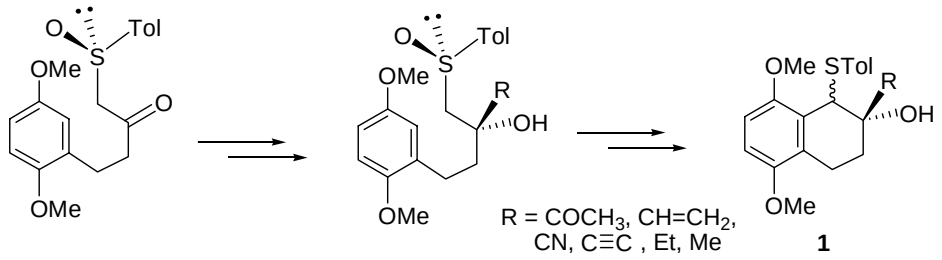
Abstract

The synthesis of two enantiomerically pure bicyclic fragments are reported, the 2-bromo dimethylhydroquinone **6** (as a precursor of the corresponding bromo-quinone) and quinone monoketal **5**. They are presumably able to control the regioselectivity in their reactions with appropriated dienes or nucleophiles, to afford the tetracyclic skeleton of chiral anthracyclinones**.**

Keywords: Chiral anthracyclinone, regioselective synthesis, quinone monoketals, sulfinyl group

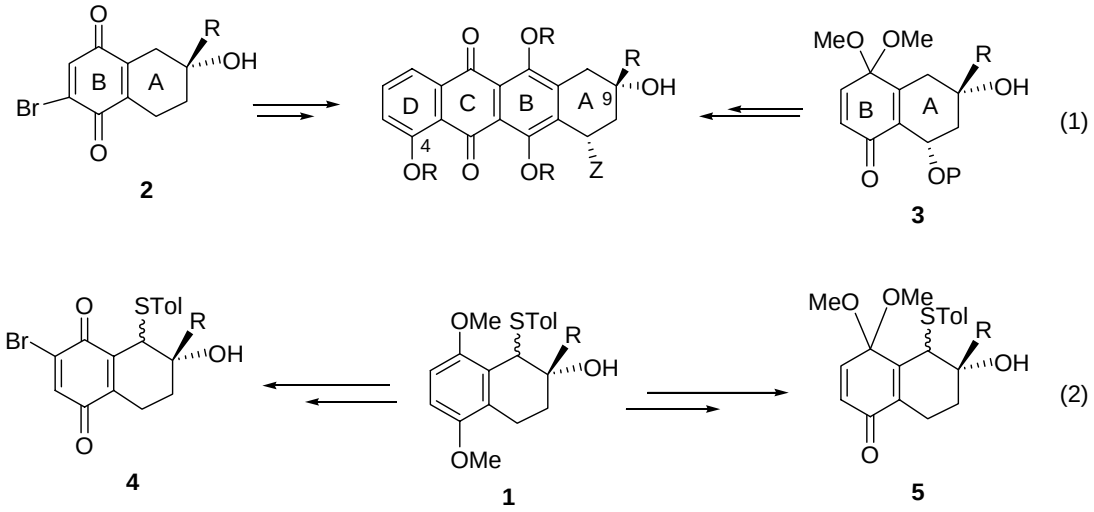
Introduction

The clinical value of the anthracyclinone antibiotics in the treatment of a large variety of human cancers[1] has increased the interest in methods for their synthesis, to improve the previously described synthesis,[2] and to prepare analogs exhibiting better properties.[3] The two main problems of the different strategies used for synthesizing anthracyclinones are related to the stereoselective construction of the A ring containing the chiral center,[4] and the regioselective preparation of the tetracyclic skeletons from bicyclic fragments.[5] In the first context we have reported a versatile method based on the use of the sulfinyl group as a chiral auxiliary for creating the tertiary carbinol in high enantiomeric excess,[6] and for achieving the intramolecular asymmetric Pummerer reaction affording the bicyclic precursors of the anthracyclinones **1** (Scheme 1).[7]



Scheme 1

The regioselective construction of the tetracyclic skeletons has been a central issue for those anthracyclinones bearing some oxygenated substituent (equation 1, Scheme 2). Many strategies have been used, those involving the coupling of bicyclic fragments containing the AB rings being among the most successful. In this context, bromoquinones[8] and quinone monoketals[9] (see **2** and **3** in Scheme 2) have shown to be efficient in controlling the regioselectivity of their reactions as dienophiles or electrophiles; however the synthetic sequences affording these intermediates are rather long. With these precedents we decided to perform the synthesis of the enantiomerically pure bromoquinone **4** and quinone monoketal **5** starting from compound **1** (equation 2, Scheme 2) making use of short synthetic sequences. The results obtained in this study are reported in this paper..

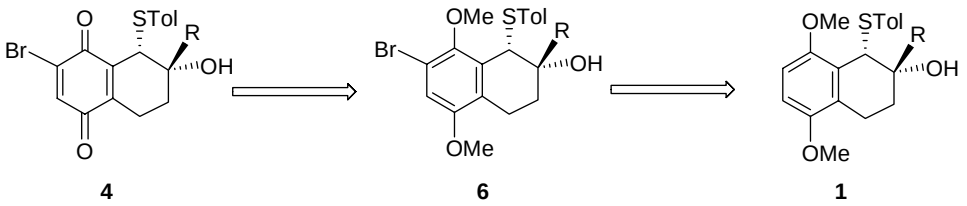


Scheme 2

Results and Discussion

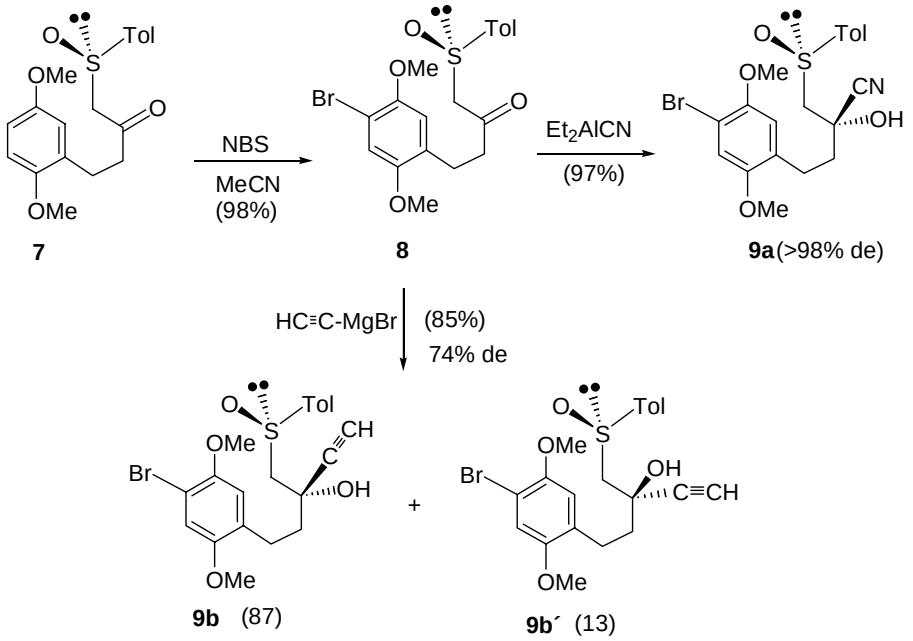
For synthesizing the bicyclic bromoquinones **4**, we first tried the strategy shown in Scheme 3 consisting in the regioselective bromination of compound **1** with NBS[10] and further oxidation of the brominated hydroquinone **6** into **4**. However, under the bromination conditions previously

reported[10] we could only detect the oxidation products of the sulfinyl group, which gave mixtures of sulfinyl hydroquinones without affecting the aromatic ring.



Scheme 3

As the NBS could not be used in the presence of the STol group, despite having shown its efficiency in the completely regioselective bromination of other monoalkyl hydroquinones,[10] we decided to perform the synthesis of **6** according to the sequence indicated in Scheme 4. This involves the bromination of the sulfoxide **7**, which had been used as precursor in the synthesis of **1** (Scheme 1), and the conversion of **8** into **6** following a sequence similar to that shown in Scheme 1.[6]

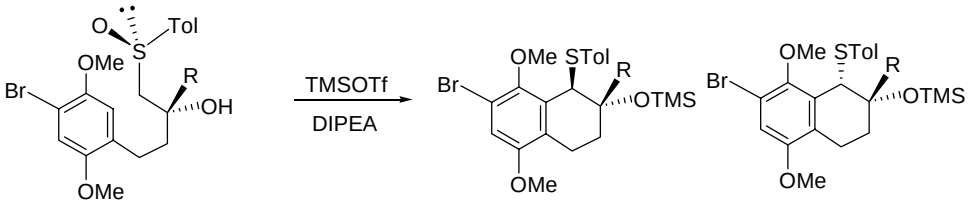


Scheme 4

Reaction of **7** with NBS in acetonitrile yielded the brominated derivative **8** in almost quantitative yield with complete regioselectivity under mild conditions (Scheme 4). In order to obtain the tertiary carbinol with the proper configuration (C-9 in the final anthracyclinones, Scheme 2), two nucleophilic reagents were added to the carbonyl group of compound **8**,

Et_2AlCN or HCCMgBr, which allow the introduction of nitrile and ethynyl groups. These could eventually be transformed easily into any of the groups present in the natural or synthetic anthracyclinones. Reaction with Et_2AlCN proceeds in a completely stereocontrolled manner, yielding a single cyanohydrin (**9a**) in almost quantitative yield. This result was predictable according to the behavior observed in the hydrocyanation of other β-ketosulfoxides.[11] The reaction of ethynyl magnesium bromide with **8** afforded a 87:13 mixture of two diastereomeric ethynylcarbinols (**9b** and **9'b**) in 85% combined yield, which could be separated by chromatography. This lower stereoselectivity was not unexpected, according to previous results concerning alkylation of β-ketosulfoxides.[12] The configurational assignment of all these compounds was performed by comparison of their spectroscopic parameters with those of the corresponding debrominated substrates reported previously.[6]

The next step was the cyclization of **9a** and **9b** under the Pummerer conditions (TMSOTf/DIPEA).[7] Mixtures of two bicyclic bromohydroquinones (**6** and **6'**), epimers at thio-substituted carbon, were obtained (Scheme 5). It is noteworthy that the stereoselectivity observed in the reaction of **9b** is very low (20% de), whereas that of the corresponding debrominated hydroquinone had been shown to be complete (de > 98%).[7] This suggests that the orientation of the methyl group (and therefore the lone electron pair) of the OMe group next to the bromine, is quite important in the stereoselectivity control of the cyclization under Pummerer conditions.



9a (R = CN)
9b (R = C≡CH)

(89% yield)
(70% yield)

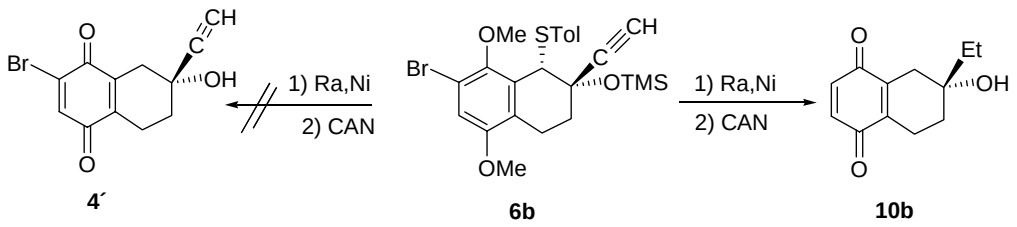
6a (87)
6b (60)

6'a (13)
6'b (40)

Scheme 5

According to Scheme 3, it was now necessary to oxidize the hydroquinones **6** into the bromoquinones **4**, but unfortunately the two reactions used so far have been unsuccessful. The oxidation of **6b** with CAN, one of the reagents used most to prepare quinones from hydroquinones,[13] afforded complex mixtures of compounds under different conditions. As the presence of the easily oxidation of the SMe group at **6b** could once more be responsible for the formation of mixtures, we decided to remove it before oxidizing the hydroquinone ring. This sequence would provide the hydroquinone **4´**, which is also appropriate for achieving the regioselective coupling with dienes or nucleophiles. The reaction of **6b** with Raney-Nickel followed by oxidation with CAN yielded compound **10b** instead of the expected **4´**, which indicates that reduction of the triple bond and hydrogenolysis of the C–Br bond is taking place simultaneously with the breaking of the C–S bond (Scheme 6). As the evolution of **9b** is not

expected to be highly regioselective, we are currently exploring other reactions allowing the synthesis of **4** or **4´** from **6**.

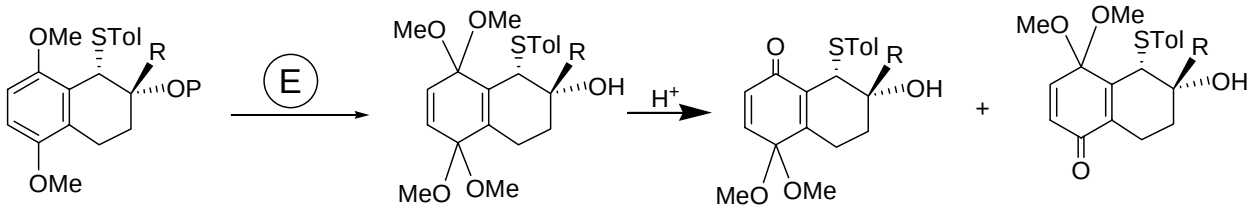


4´ **6b** **10b**

Scheme 6

As these substrates can be prepared by oxidation of hydroquinone mono-ethers[14] we first tried to obtain these compounds by partial hydrolysis of the hydroquinones **1.** However, after trying these substrates with various reagents (MeSLi/DMF, 100 ºC; EtSH/$AlCl_3$, 0 ºC; $AlCl_3$/$PhNO_2$) described in the literature[15] as being efficient for transforming aromatic ethers into phenols, no successful result was obtained, presumably owing to interferences of the reagents with the substituents at the chiral carbon.

We then tried to obtain quinone monoketals by regiocontrolled partial hydrolysis of their corresponding bis-ketals, which in their turn could be obtained by anodic oxidation of the hydroquinone derivatives.[16] The substrates studied and the results obtained in these transformations are indicated in Scheme 7.



1a	(R = H; P = H)	**11a** (50%)	**12a** (75)	**12'a** (25)
1b	(R = Me; P = H)	**11b** (80%)	**12b** (75)	**12'b** (25)
1c	(R = CCH; P = TMS)	**11c** (85%)	**12c** (75)	**12'c** (25)
1d	(R = COMe; P = TMS)	**11d** (97%)	**12d** (72)	**12'd** (28)

Scheme 7

Anodic oxidation of hydroquinones **1a–d** [6,7] was performed at 0 ºC using the pair Pt (anode) / Cu (cathode) in methanolic KOH (2%) and 100 mA (direct current).[16] The bis-ketals **11a–d** were obtained as dark oils with yields ranging between 50% and 97%, with the best results obtained for tertiary alcohol derivatives. Under the anodic oxidation conditions TMS derivatives are

transformed into the free alcohols. Compounds **11a–d** were used in the further step without prior purification.

The partial hydrolysis of the bis-ketals into their corresponding monoketals was not an easy task because of the ease of the total hydrolysis into quinone rings. A number of mild conditions was tried. AcOH (5%)[17] in acetone at –20 ºC for 12 hours provides 75:25 mixtures of monoketals **12** and **12'** starting from **11a–c**. After chromatographic separation of the mixtures, by using silica gel previously deactivated with Et_3N (5%), the major regioisomers **12** were obtained in 40% yield. Lower regioselectivity was obtained from **11d** with acetic-[17] or oxalic acid[18] in acetone for 1 hour (62:38 mixtures of **12d** and **12'd**). Under milder conditions (acetone/water, RT, 3 days), a 72:28 mixture of **12d** and **12'd** was obtained, with the major mono-ketal being isolated in 30% yield after chromatographic purification.

The major regioisomers (**12**) exhibit δ values for the α- and β- protons which are slightly higher and lower, respectively, than those for the minor regioisomers (**12'**). Thus, the Δδ values for the olefinic protons [δH(β) - δH(α)] are always lower for **12**. The structural assignment of both regioisomers was made by assuming that the sulfur function should retard the hydrolysis of its nearest acetal group by steric effects.[19] The unequivocal assignment of the regioisomers was made for compounds **12a** and **12'a** by studying the coupling between the proton at C-1 and the carbonyl carbon. Only compound **12a** exhibited such a vicinal coupling constant ($^3J_{H,CO}$ = 3.0 Hz), which was absent in compound **12'a**.

In summary, we have described the synthesis of enantiomerically pure bicyclic intermediates which are potentially useful for synthesizing anthracyclinones in a highly regioselective way. Bicyclic mono-ketals containing the A/B rings of the tetracyclic skeletons were obtained by partial hydrolysis of the corresponding bis-ketals resulting in the anodic oxidation of the hydroquinones. Precursors of the bicyclic bromoquinones have also been prepared. The reactions of these bicyclic intermediates with the appropriate fragments as precursors of the C/D rings of tetracyclic skeletons are currently being studied and the results will be reported in the due course.[20]

Experimental Section

General Procedures. All moisture-sensitive reactions were performed in flame–dried glassware equipped with rubber septa under positive pressure of argon. Silica gel 60 (230–400 mesh ASTM) and DC-Alufolien 60 F_{254} were used for flash column chromatography and analytical TLC, respectively. Melting points were determined in a Gallenkamp apparatus in open capillary tubes. Microanalyses were performed with Perkin Elmer 2400 CHN and Perkin Elmer 2400 C-10II CHNS/O analyzers. NMR spectra were determined in $CDCl_3$ solutions, unless otherwise indicated, at 300 and 75 MHz for ^{1}H- and ^{13}C- NMR respectively; chemical shifts (δ) are reported in ppm and *J* values are given in Hertz. The IR spectra frequencies are given in cm^{-1}. RT denotes room temperature.

[(S)*R*]-4-(4-Bromo-2,5-dimethoxyphenyl)-1-*p*-tolylsulfinylbutan-2-one (8). To a solution of 2.56 g of β-ketosulfoxide **7** in 50 mL of CH_3CN was added 1.45 g of NBS (8.2 mmol) at RT. The reaction was monitored by TLC and when the reaction was finished (1 h), the solvent was evaporated. To the resulting mixture was added 10 mL of CCl_4, to deposit a white solid. This solid was removed by filtration, and the solvent was recovered. Finally, the solvent was evaporated under reduced pressure, giving 3.1 g of **8**. Yield quantitative. White solid, mp 135–136 ºC (ethyl acetate). $[\alpha]_D^{20}$ +134 (*c* 0.1, $CHCl_3$). IR (KBr) 2954, 2864, 2249, 1645, 1490, 1448, 1376, 1304, 1237, 1118, 1072, 889 cm^{-1}. ^{1}H- NMR (200 MHz): 7.45 and 7.29 (AA'BB' system, *J* 8.2 Hz, 4H), 6.99 (s, 1H), 6.73 (s, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.83 (d, *J* 13.4 Hz, 1H), 3.70 (d, *J* 13.4 Hz, 1H), 2.79–2.77 (m, 4H), 2.41 (s, 3H).^{13}C- NMR (50 MHz): 200.8, 151.6, 149.7, 142.0, 139.4, 130.0 (2C), 128.7, 123.9, 115.5, 114.8, 67.8, 56.8, 55.8, 44.6, 24.4, 21.4. Anal. Calcd. for $C_{19}H_{21}BrO_4S$: C, 53.77; H, 4.99; S, 7.54. Found: C, 53.25; H, 4.87; S, 7.07.

[2*S*,(S)*R*]-4-(4-Bromo-2,5-dimethoxyphenyl)-2-hydroxy-2-*p*-tolylsulfinylmethylbutane nitrile (9a). A solution of **8** (3.5 g, 8.5 mmol) in 30 mL of dry THF was added dropwise to Et_2AlCN (17 mL, 17 mmol, 1 M in toluene) under argon atmosphere at -35 °C. The mixture was stirred for 5 min and then transferred via cannula into 60 mL of MeOH/conc. HCl, 1/1, at –78 °C. The resulting mixture was stirred for 15 min and poured carefully into 200 g of ice with 30 mL of conc. HCl, CH_2Cl_2 (50 mL) was added and the layers were separated. The aqueous phase was extracted with 2x50 mL of CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure, yielding pure **9a** (3.9 g, 97% yield) as a colorless oil. $[\alpha]_D^{20}$ +111 (*c* 0.1, $CHCl_3$). ^{1}H- NMR (200 MHz): 7.58 y 7.39 (AA´BB´ system, *J* 6.8 Hz, 4H), 7.01 (s, 1H), 6.76 (s, 1H), 6.05 (bs, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.07 (d, *J* 12.9 Hz, 1H), 2.95–2.90 (m, 3H), 2.45 (s, 3H), 2.12–2.07 (m, 2H). ^{13}C- NMR (50 MHz): 151.7, 150.0, 143.1, 138.9, 130.5, 123.9, 119.3, 115.8, 114.5, 111.7, 111.1, 70.8, 62.4, 56.9, 55.9, 41.0, 24.9, 21.4. Anal. Calcd. for $C_{20}H_{22}BrNO_4S$: C, 53.10; H, 4.90; S, 7.09. Found: C, 53.12; H, 4.82; S, 7.01.

[3*S*,(S)*R*]-5-(4-Bromo-2,5-dimethoxyphenyl)-3-*p*-tolylsulfinylmethylpent-1-in-3-ol (9b). A solution of **8** (0.5 g, 1.4 mmol) in 30 mL of dry toluene was added dropwise to H-C≡C-MgBr (5.6 mmol, 0.5 M in toluene) under argon at RT. The reaction was followed by TLC, and when finished saturated NH_4Cl (5 mL) was added. The crude mixture was extracted with CH_2Cl_2 (2x10 mL), and separated from the aqueous phase. Finally the organic phase was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. A mixture of diastereoisomers **9b** and **9b'** (87:13) was obtained, which was separated by chromatography (eluent: hexane/AcOEt 7/3). Major diastereoisomer (**9b**): yield 70%. White solid. mp 140–141 ºC (ethyl acetate). $[\alpha]_D^{20}$ +118 (*c* 0.5, $CHCl_3$). ^{1}H- NMR (300 MHz): 7.57 and 7.34 (AA´BB´ system, *J* 8.7 Hz, 4H), 6.97 (s, 1H), 6.74 (s, 1H), 5.33 (bs, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.05 (d, *J* 12.9 Hz, 1H), 2.87 (d, *J* 12.9 Hz, 1H), 2.80 (s, 1H), 2.85–2.79 (m, 2H), 2.42 (s, 3H), 2.02–1.95 (m, 2H). ^{13}C-NMR(50 MHz): 151.8, 149.9, 142.2, 140.1, 130.2, 129.8, 123.9, 115.8, 115.7, 108.7, 83.9, 75.3, 69.7, 65.3, 56.9, 56.0, 42.5, 24.9, 21.4. MS (EI) *m/z* 452 (8), 450 (8), 435 (9), 433 (10), 410 (9), 408 (9), 243 (27), 241 (27), 231 (100), 229 (96), 214 (20), 198 (32), 140 (42), 124 (39), 91 (81),

77 (39). The minor diastereoisomer (**9b'**) could not be separated from the starting material **8**. ^{1}H-NMR (300 MHz): 7.52 and 7.25 (AA´BB´ system, *J* 8.7 Hz, 4H), 7.01 (s, 1H), 6.77 (s, 1H), 4.45 (bs, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.26 (d, *J* 12.9 Hz, 1H), 3.03 (d, *J* 12.9 Hz, 1H), 2.95–2.70 (m, 2H), 2.61 (s, 1H), 2.42 (s, 3H), 2.30–2.20 (m, 2H).

(1*R*,2*S*)-7-Bromo-2-cyano-5,8-dimethoxy-1-*p*-tolylsulfenyl-2-trimethylsilyloxy-1,2,3,4-tetrahydronaphthalene (6a). To a solution of **9a** (1.4 g, 3.0 mmol) in 30 mL of dry CH_2Cl_2 under argon atmosphere at 0°C was added TMSOTf (2.6 mL, 13.5 mmol) and *i*-Pr_2NEt (2.4 mL, 13.5 mmol). The cold bath was removed and the mixture stirred for 30 min. The mixture was transferred via cannula into a saturated aqueous solution of $NaHCO_3$. The organic phase was separated and extracted with 2x10 mL of CH_2Cl_2. The organic phases were combined and washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Purification by flash chromatography (hexane/AcOEt, 14/1) yielded **6a** (1.4 g, 3.0 mmol) as a mixture of epimers at C-1 (83/17). Yield 89%. Major isomer (**6a**): $[\alpha]_D^{20}$ +115.4 (*c* 1.1, $CHCl_3$). ^{1}H- NMR (200 MHz): 7.53 and 7.14 (AA´BB´ system, *J* 8.0 Hz, 4H), 7.01 (s, 1H), 4.93 (d, *J* 2.1 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.00–2.60 (m, 3H), 2.33 (s, 3H), 2.22–2.17 (m, 1H), 0.1 (s, 9H). ^{13}C-NMR (50 MHz): 153.4, 148.6, 137.0, 133.0, 131.5, 131.3, 129.7, 123.5, 120.4, 113.7, 71.9, 61.3, 55.6, 54.0, 29.3, 21.9, 21.0, 1.0. Minor isomer (**6a'**): 7.46 and 7.10 (AA´BB´, *J* 8.0 Hz, 4H), 6.91 (s, 1H), 4.65 (d, *J* 2.14 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.00–2.60 (m, 3H), 2.33 (s, 3H), 2.35–2.15 (m, 1H), 0.1 (s, 9H, TMS).

(1*R*,2*S*)-7-Bromo-2-ethynyl-5,8-dimethoxy-1-*p*-tolylsulfenyl-2-trimethylsilyloxy1,2,3,4-tetrahydronaphthalene (6b). To a solution of **9a** (1.4 g, 3.0 mmol) in 30 mL of dry CH_2Cl_2 under argon at 0 °C was added TMSOTf (2.6 mL, 13.5 mmol) and *i*-Pr_2NEt (2.4 mL, 13.5 mmol). The cold bath was removed and the mixture was stirred for 30 min, and transferred via cannula into a saturated aqueous solution of $NaHCO_3$. The organic phase was separated and the aqueous phase extracted with 2x10 mL of CH_2Cl_2. The organic phases were combined and washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*, yielding **6b** (1.4 g, 2.1 mmol) as a mixture of unseparable epimers at C-1 (40/60). Yield 70%. Major isomer (**6b**): ^{1}H- NMR (300 MHz): 7.46 and 7.07 (AA´BB´ system, *J* 7.8 Hz, 4H), 6.87 (s, 1H), 4.86 (d, *J* 2.4 Hz, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 2.70–2.40 (m, 3H), 2.32 (s, 3H), 2.30 (s, 1H), 2.05–1.90 (m, 1H), 0.07 (s, 9H, TMS). Minor isomer (**6b'**): 7.46 and 7.07 (AA´BB´ system, *J* 7.8 Hz, 4H), 6.86 (s, 1H), 4.66 (d, *J* 2.1 Hz, 1H), 3.77 (s, 6H), 2.70–2.40 (m, 3H), 2.32 (s, 3H), 2.30 (s, 1H), 2.05–1.90 (m, 1H), 0.04 (s, 9H, TMS).

(*R*)-6-Ethyl-6-hydroxy-5,6,7,8-tetrahydronaphthalene-1,4-dione (10b). To a solution of **6b** (282 mg, 0.55 mmol) in 5 mL of EtOH under argon, was added an excess of Ra-Ni (previously activated). After 1 hour, it was filtered (Celite®), and the organic phase evaporated under reduce pressure. To a solution of this crude mixture in 6 mL of CH_3CN, it was added 1.1 mmol of CAN in 2 mL of water. After 5 min. 10 mL of CH_2Cl_2 and 5 mL of water was added. The organic- and aqueous phases were separated, washed with saturated NaCl, and finally dried over Na_2SO_4. The solvent was eliminated under reduced pressure, and chromatographed (eluent, hexane/AcOEt 7/3), giving 91 mg of **10b** as a colorless oil. Yield 80%, $[\alpha]_D^{20}$ –164.7 (*c* 0.44, $CHCl_3$). IR (film)

3528 (OH), 2968, 1665 (CO) cm^{-1}. ^{1}H- NMR (300 MHz) δ: 6.71 (s, 2H), 2.40 (bs, 1H), 2.65–2.30 (m, 4H), 1.84–1.80 (m, 1H), 1.63–1.58 (m, 3H), 1.03 (t, *J* 7.2 Hz, 3H). ^{13}C- NMR (75 MHz): 187.3, 187.0, 141.8, 139.9, 136.4, 136.3, 69.7, 34.9, 34.5, 31.2, 20.0, 7.3. MS (EI) *m/z* 206 (M^+, 48), 177 (96), 148 (100), 131 (26), 107 (23).

General method for obtaining the bis-dimethyl acetals of the benzoquinones 11

To a solution of the corresponding dimethoxyquinone **1** in 175 mL of MeOH was added a solution of KOH (2g) in 25 mL of MeOH at 0 ºC. This solution was subjected to anodic oxidation, using a Pt/Cu couple at 100 mA. The reaction was followed by TLC, and when it was complete, MeOH was evaporated under reduced pressure. The crude mixture was dissolved in 20 mL of CH_2Cl_2 and washed with 10 mL of water. Finally, the organic phase was dried over anhydrous Na_2SO_4, and the solvent eliminated under vacuum. The product **11** was used without further purification.

(1*S*,2*R*)-5,5,8,8-Tetramethoxy-1-*p*-tolylsulfenyl-1,2,3,4,5,8-hexahydronaphthalen-2-ol. Obtained using the general method from **1a**, affording **11a**. Reaction time: 10 minutes. Yield 50%. ^{1}H- NMR (200 MHz): 7.51 and 7.08 (AA'BB' system, *J* 8.1 Hz, 4H), 6.17 (s, 2H), 4.20–4.15 (m, 1H), 3.84 (tt, *J* 11.5, 4.0 Hz, 1H), 3.48–3.43 (m, 1H), 3.26 (s, 3H), 3.20 (s, 3H), 3.18 (s, 3H), 3.13 (s, 3H), 2.65 (d, *J* 11.3 Hz, 1H), 2.37–2.33 (m, 1H), 2.31 (s, 3H), 2.0–1.8 (m, 2H). ^{13}C-NMR (50 MHz):138.8, 136.5, 134.8, 133.8, 132.6, 131.5, 130.8, 129.6, 95.7, 95.2, 68.8 (2C), 51.6, 51.4, 50.9, 50.6, 26.9, 21.9, 20.9.

(1*S*,2*R*)-2-Methyl-5,5,8,8-tetramethoxy-1-*p*-tolylsulfenyl-1,2,3,4,5,8-hexahydronaphthalen-2-ol. (11b). Obtained using the general method from **1b**, affording **11b**. Reaction time: 10 minutes. Yield 80%. ^{1}H- NMR (200 MHz): 7.50 and 7.10 (AA´BB´ system, *J* 8.3 Hz, 4H), 6.22 (d, *J* 10.8 Hz, 1H), 6.10 (d, *J* 10.8 Hz, 1H), 5.63 (bs, 1H), 3.33 (s, 3H), 3.21 (s, 6H), 3.20 (s, 3H), 3.00–2.70 (m, 5H), 2.33 (s, 3H), 2.16 (s, 3H).

(1*S*,2*R*)-2-Ethynyl-5,5,8,8-tetramethoxy-1-*p*-tolylsulfenyl-1,2,3,4,5,8-hexahydronaphthalen-2-ol. (11c). Obtained using the general method from **1c**, affording **11c**. Reaction time: 60 minutes. Yield 85%. ^{1}H- NMR (300 MHz): 7.53 (d, *J* 9.0 Hz, 2H), 7.09 (d, *J* 9.0 Hz, 2H), 6.19 (s, 2H), 4.22 (s, 1H), 3.24 (s, 6H), 3.22 (s, 3H), 3.20 (s, 3H), 2.52–2.48 (m, 2H), 2.36 (s, 1H), 2.29 (s, 3H), 2.05–1.95 (m, 2H).^{13}C NMR (75 MHz): 139.2, 137.1, 134.1, 133.2, 131.8, 131.4, 131.0, 129.7, 95.8, 95.2, 84.7, 77.2, 72.6, 57.3, 51.5 (2C), 51.1 (2C), 31.8, 22.1, 21.0.

(1*S*,2*R*)-2-Acetyl-5,5,8,8-tetramethoxy-1-*p*-tolylsulfenyl-1,2,3,4,5,8-hexahydronaphthalen-2-ol. (11d). Obtained using the general method from **1d**, affording **11d**. Reaction time: 60 minutes. Yield 97%. ^{1}H- NMR (200 MHz): 7.52 and 7.09 (AA´BB´system, *J* 8.6 Hz, 4H), 6.25 (d, *J* 10.7 Hz, 1H), 6.08 (d, *J* 10.7 Hz, 1H), 4.31 (d, *J* 2.1 Hz, 1H), 3.24 (s, 3H), 3.23 (s, 3H), 3.20 (s, 3H), 3.06 (s, 3H), 2.40–2.10 (m, 3H), 2.33 (s, 3H), 2.23 (s, 3H), 2.05–2.00 (m, 1H).

General methods for the hydrolysis of the bis(dimethyl)ketal of benzoquinones 11

Method 1. To a solution of the corresponding bis-ketal **11** (0.1 mmol) in 1 mL of acetone at –30 ºC, was added 0.5 mL of AcOH (5%). After 2 hours Et_2O was added, and washed with

saturated $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and the solvent eliminated under reduced pressure. Both regioisomers could be separated by chromatography (eluent hexane/AcOEt 7/3) using previously neutralized silica gel (12 h in hexane with 5% Et_3N).

Method 2. The corresponding bis-ketal **11** (0.1 mmol) was dissolved in a mixture of 2/1 acetone/water during 3 days. Then, the solvent was eliminated, and the crude mixture dissolved in CH_2Cl_2, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The two regioisomers were separated by chromatography (eluent; hexane/AcOEt 7/3), on previously neutralized silica gel (12 h in hexane with 5% of Et_3N).

(7*R*, 8*S*)-7-Hydroxy-4,4-dimethoxy-8-*p*-tolylsulfenyl-5,6,7,8-tetrahydro-4*H*-naphthalen-1-one (12a/12a′). Obtained from the quinone bis-ketal **11a** (40.5 mg, 0.1 mmol) in 1 mL of acetone by Method 1, as a 5/1 mixture of **12a**/**12a'**. Major isomer (**12a**): Yield 42%. ^{1}H- NMR (200 MHz): 7.57 and 7.12 (AA´BB´ system, *J* 8.2 Hz, 4H), 6.76 (d, *J* 10.1 Hz, 1H), 6.48 (d, *J* 10.1 Hz, 1H), 4.48–4.40 (m, 1H), 3.90–3.80 (m, 1H), 3.21 (s, 3H), 3.17 (s, 3H), 2.55 (ddd, *J* 19.5, 6.3, 2.0 Hz, 1H), 2.34 (s, 3H), 2.34–2.28 (m, 1H), 2.15–2.08 (m, 1H), 2.05–1.98 (m, 1H), 1.82 (td, *J* 11.7, 6.24 Hz, 1H).^{13}C- NMR (50 MHz): 182.5, 151.2, 143.2, 137.7 (2C), 135.6, 132.4, 132.3, 129.8, 94.8, 68.4, 51.0, 50.1, 50.7, 26.8, 23.3, 21.1. Minor isomer (**12a'**): Yield 10%. ^{1}H- NMR (200 MHz): 7.52 and 7.12 (AA´BB´ system, *J* 8.2 Hz, 4H), 6.79 (d, *J* 10.1 Hz, 1H), 6.41 (d, *J* 10.2 Hz, 1H), 4.27–4.22 (m, 1H), 3.90–3.80 (m, 1H), 3.27 (s, 3H), 3.17 (s, 3H), 2.73 (d, *J* 11.3 Hz, 1H), 2.67–2.64 (m, 1H), 2.36 (s, 3H), 2.36–2.32 (m, 1H), 2.06–2.02 (m, 1H), 1.86–1.82 (m, 1H).

(7*R*,8*S*)-7-Hydroxy-4,4-dimethoxy-7-methyl-8-*p*-tolylsulfenyl-5,6,7,8-tetrahydro-4*H*-naphthalen-1-one (12b/12b′). Obtained from the quinone bis-ketal **11b** following method 1, yielding a 3/1 mixture of regioisomers of **12b**/**12b'**. Major isomer (**12b**): Yield 40%. IR (film): 1620 (CO), 1570, 900 cm^{-1}; ^{1}H- NMR (200 MHz): 7.50 and 7.13 (AA'BB' system, *J* 7.9 Hz, 4H), 6.70 (d, *J* 10.3 Hz, 1H), 6.43 (d, *J* 10.3 Hz, 1H), 5.63 (s, 1H), 3.20 (s, 3H), 3.19 (s, 3H), 3.00–2.80 (m, 2H), 2.68–2.63 (m, 2H), 2.33 (s, 3H), 2.11 (s, 3H). Minor isomer (**12b'**): this compound was unstable towards silica gel.

(7*S*,8*S*)-7-Ethynyl-7-hydroxy-4,4-dimethoxy-8-*p*-tolylsulfenyl-5,6,7,8-tetrahydro-4*H*-naphthalen-1-one (12c/12c′). Obtained as the major isomer in a mixture 75/25 of regioisomers **12c**/**12c'** following Method 1, starting from the quinone bis-ketal **11c**. Major isomer (**12c**): Yield: 37%. ^{1}H- NMR (200 MHz): 7.58 and 7.12 (AA'BB' system, *J* 8.1 Hz, 4H), 6.72 (d, *J* 10.5 Hz, 1H), 6.50 (d, *J* 10.5Hz, 1H), 4.52 (s, 1H), 3.23 (s, 3H), 3.19 (s, 3H), 2.98 (s, 1H), 2.64–2.58 (m, 2H), 2.35 (s, 1H), 2.33 (s, 3H), 2.12–2.05 (m, 2H). Minor isomer (**12c'**): Yield: 11%. ^{1}H NMR (200 MHz): 7.73 and 7.32 (AA'BB' system, *J* 8.1 Hz, 4H), 6.80 (d, *J* 10.3 Hz, 1H), 6.43 (d, *J* 10.3 Hz, 1H), 4.46 (s, 1H), 3.35 (s, 3H), 3.19 (s, 3H), 2.72–2.68 (m, 2H), 2.4 (s, 3H), 2.30 (s, 1H), 2.30–2.26 (m, 2H).

(7S,8*S*)-7-Acetyl-7-hydroxy-4,4-dimethoxy-1-*p*-tolylsulfenyl-5,6,7,8-tetrahydro-4*H*-naphthalen-1-one (12d/12d'). Obtained by Method 2, yielding a mixture of regioisomers **12d**/**12d′** (72/28). Major isomer (**12d**): Yield 30%. ^{1}H- NMR (200 MHz): 7.56 and 7.14

(AA´BB´ system, *J* 8.1 Hz, 4H), 6.70 (d, *J* 10.2 Hz, 1H), 6.50 (d, *J* 10.2 Hz, 1H), 4.50–4.26 (m, 1H), 3.37 (bs, 1H), 3.19 (s, 3H), 3.10 (s, 3H), 2.58–2.54 (m, 1H), 2.33 (s, 3H), 2.27–2.24 (m, 1H), 2.22 (s, 3H), 2.07–2.04 (m, 1H), 1.94–1.90 (m, 1H).^{13}C- NMR (50 MHz): 208.3, 182.3, 150.6, 143.6, 138.3, 135.8, 132.6, 132.4, 131.5, 130.0, 95.1, 77.7, 51.2, 51.1, 51.0, 28.7, 24.8, 22.1, 21.1. Minor isomer (**12d'**): Yield 10%; ^{1}H- NMR (200 MHz): 7.51 and 7.14 (AA´BB´ system, *J* 8.1 Hz, 4H), 6.82 (d, *J* 10.2 Hz,1H), 6.38 (d, *J* 10.2 Hz, 1H), 4.30 (d, *J* 2.1 Hz, 1H), 3.25 (s, 3H), 3.20 (s, 3H), 2.52–2.48 (m, 2H), 2.33 (s, 3H), 2.27–2.24 (m, 1H), 2.22 (s, 3H), 2.17–2.14 (m, 2H), 1.42–1.36 (m, 1H).

1,3-Dihydro-7-methoxy-3-oxo isobenzofuran-1-carbonitrile (13). Synthesized following ref. 20. ^{1}H-NMR (200 MHz): 7.65 (dd, *J* 7.5, 6.9 Hz, 1H), 7.53 (d, *J* 7.5 Hz, 1H), 7.24 (d, *J* 6.9 Hz, 1H), 5.98 (s, 1H) 4.01 (s, 3H).

Acknowledgements

We thank the Spanish Government for financial support (Grant BQU2003-04012). J.A. thanks the Ministerio de Ciencia y Tecnología for a predoctoral fellowship.

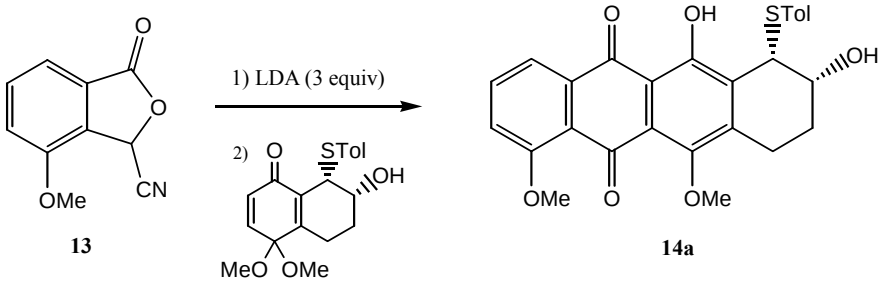
References and Footnotes

1. (a) DeVita, J. V. T.; Hellman, S.; Rosemberg, S. A. Eds; *Cancer, Principles and Practice of Oncology*; J. B. Lippincott Company: Philadelphia, 1993. (b) Arcamone, C. *Topics in Antibiotic Chemistry*; Ellis Horwood: Chichester, England, 1978; Vol. 2, p 99. (c) Remer, W. A. *The Chemistry of Antitumor Antibiotics*; John Wiley & Sons: New York, 1979; Vol. 1, p 63. (d) Arcamone, F. *Anticancer Agents Based on Natural Product Models*; Academic Press: New York, 1980; p. 1. (e) Cassinelli, G.; Ballabio, M.; Arcamone, F.; Casazza, A. M.; Podesta, A. *J. Antibiot.* **1985**, *38*, 856. (f) Hermentin, P.; Doenges, R.; Gronski, P.; Bosslet, K.; Kraemer, H. P.; Hoffmann, D.; Zilg, H.; Steinstraesser, A.; Schwarz, A. *Bioconjugate Chem.* **1990**, *1*, 100.
2. For asymmetric synthesis of anthracyclinones see: (a) Cousson, A.; Le Gouadec, G.; Monneret, C.; Florent, J. *J. Che*m. *Soc., Chem. Commun*. **1993**, 388. (b) Fujioka, H.; Yamamoto, H.; Annoura, H.; Maeda, H.; Kita, Y. *Chem. Pharm. Bull*. **1992**, *40*, 32. (c) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 10807. (d) Hauser, F.; Tommasi, R. *J. Org. Chem*. **1991**, *56*, 5758. (e) Davis, F. A.; Kumar, A.; Chen, B.-C. *Tetrahedron Lett*. **1991**, *32*, 867. (f) Tomioka, K.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1921. (g) Krohn, K. *Angew. Chem., Int. Ed.* **1986**, *25*, 790. (h) Suzuki, M.; Kimura, Y.; Terashima, S. *Tetrahedron Lett.* **1985**, *26*, 6481. (i) Sodeoka, M.; Iimori, T.; Shibasaki, M. *Tetrahedron Lett.* **1985**, *26*, 6497. (j) Suzuki, M.; Kimura, Y.;

Terashima, S. *Chem. Lett.* **1985**, 3, 367. (k) Meyers, A. I.; Higashimaya, K. *J. Org. Chem.* **1987**, *52*, 4592. (k) Domínguez, D.; Cava, P. M.; *J. Org. Chem.* **1983**, *48*, 2820.

3. (a) Oki, T.; Matsuwaza, Y.; Yoshimoto, A.; Numata, K.; Kitamura, I.; Hori, S.; Takamatsu, A.; Umezawa, H.; Ishizuka, M.; Naganawa, H.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1975**, *28*, 830. (b) Ubukata, M.; Tanaka, C.; Osada, H.; Isono, K. *J. Antibiot.* **1991**, *44*, 1274. (c) Nozaki, Y.; Hida, T.; Iinuma, S.; Ishii, T.; Sudo, K.; Muroi, M.; Kanamaru, T. *J. Antibiot.* **1993**, *46*, 569. (d) Ishigami, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1994**, *47*, 1219. (e) Xuan, L. J.; Xu, S. H.; Zhnag, H. L.; Xu, Y. M. *J. Antibiot.* **1992**, *45*, 1974. (f) Krohn, K. *Eur. J. Org Chem.* **2002**, *8*, 1351. (g) Hottop, T.; Gutke, H.-J.; Murahashi, S.-I. *Tetrahedron Lett.* **2001**, *42*, 3343.
4. (a) Rao, A. V.; Deshpande, V. H.; Laxma Reddy, N. L. *Tetrahedron Lett.* **1980**, *21*, 2661. (b) Wiseman, J. R.; French, N. I.; Hallmark, R. K.; Chiong, K. G. *Tetrahedron Lett.* **1978**, *19*, 3765. (c) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Lett.* **1984**, 1543. (d) Blade, R. J.; Hodge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 85. (e) Kende, A. S.; Curran, D. D.; Tsay, Y.-G.; Mills, J. E. *Tetrahedron Lett.* **1977**, 3537. (f) May, W.; Philips, R. S. *J. Am. Chem. Soc.* **1980**, *102*, 5983. (g) Krohn, K.; Radeloff, M. *Chem. Ber.* **1978**, *111*, 3823. (h) Boeckman, R. K. Jr.; Sum, F.-W. *J. Am. Chem. Soc.* **1982**, *104*, 4604. (i) Krohn, K.; Priyono, W. *Tetrahedron* **1984**, *40*, 4609.
5. For Friedel–Crafts approaches, see: (a) Kende, A. S.; Belletire, J. L.; Bentley, T. J.; Hume, H.; Airey, J. *J. Am. Chem. Soc.* **1975**, *97*, 4425. (b) Confalone, P. N.; Pizzolato, G. *J. Am. Chem. Soc.* **1981**, *103*, 4251. (c) Kimball, S. D.; Kim, K. S.; Mohantin, D. K.; Vanotti, E.; Johnson, F. *Tetrahedron Lett.* **1982**, *23*, 3871. (d) Achmatowicz, O.; Szechner, B. *J. Org. Chem.* **2003**, *68*, 2398. For anionic approaches, see: (e) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555. (f) Li, T.; Walsgrove, T. C. *Tetrahedron Lett.* **1981**, *21*, 3741. (g) Hauser, F. M.; Chakrapani, S.; Ellenberger, W. P. *J. Org. Chem.* **1991**, *56*, 5248. For Diels-Alder aproach see: (h) Kerdesky, F. A. J.; Ardecky, R. J.; Lakshmikantham, W. V. Cava, M. P.; *J. Am. Chem. Soc.* **1981**, *103*, 1992. (i) Brassard, P.; Savard, J. *Tetrahedron Lett.* **1979**, 4911; (j) Krohn, K.. Tolkiehn, K. *Chem. Ber.* **1980**, *113*, 2976.
6. García Ruano, J. L.; García Paredes, C.; Hamdouchi, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2935.
7. García Ruano, J. L.; García Paredes, C. *Tetrahedron Lett.* **2000**, *41*, 261.
8. (a) Kametani, T.; Takeshita, M.; Nemoto, H.; Fukumoto, F. *Chem. Pharm. Bull.* **1978**, *26*, 556. (b) Gessaon, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 3351. (c) Tamura, Y.; Annoura, H.; Yamamoto, H.; Kondo, H.; Kita, Y.; Fujioka, H. *Tetrahedron Lett.* **1987**, *28*, 5709.
9. (a) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. (b) Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 3837. (c) Mitchell, A. S.; Russell, R. A. *Tetrahedron* **1995**, *51*, 5207.
10. (a) Carreño, M. C.; García Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328.

11. (a) García Ruano, J. L.; Martín Castro, A. M.; Rodríguez, J. H. *Tetrahedron Lett*. **1991**, *32*, 3195. (b) García Ruano, J. L.; Martín Castro, A. M.; Rodriguez, J. H *Recent Res. Devel. Organic. Chem*. **2004**, *4*, 261.
12. Bueno A. B.; Carreño, M. C.; García Ruano, J.:L. *An. Chem*. **1994**, *90*, 442. and references therein.
13. Carreño, M. C.; Fernández-Mudarra, G.; Merino, E.; Ribagorda, M. *J. Org. Chem.* **2004**, *69*, 3413 and references therein.
14. Kuwahara, S.; Saito, M. *Tetrahedron Letters* **2004**, *45*, 5047.
15. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis;* 3rd Edn; John Wiley and Sons, 1999.
16. Swenton, J.; Rynolds, P. *J. Am. Chem. Soc*. **1978**, *100*, 6188.
17. Chen, C.-P.; Swenton, J. S. *J. Org. Chem*. **1985**, *50*, 4569.
18. Evans, D. A.; Tanis, S. P.; Hart, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5813.
19. According to this assumption, the regioselectivity would increase with the size of the function at C-1. In order to confirm the assumption and thus increase the regioselectivity, the sulfone derived from **3** was prepared. However, its anodic oxidation into the corresponding bis-ketal was totally unfruitful (only decomposition products were obtained).
20. Preliminary results obtained in reaction of **12a** with compound **13** (Frescos, J. N.; Swenton, J. S. *J. Chem. Soc*., *Chem. Commun*. **1985**, 658) showed a completely regioselective evolution of this monoketal, yielding the tetracyclic compound **14a** in 50% yield (^{1}H-NMR) whose purification is not easy (decomposition of compound **14a** was observed in our hands). Optimization of this process as well as the study of the reactions of other monoketals containing the tertiary carbinol in the right configuration are in progress.



13 **12a** **14a**