Improved synthesis of 5-(*t*-butyldimethylsilyloxymethyl)-2-methyl-5,6-dihydrocyclopenta[*c*]pyrrole-1,3(2*H*,4*H*)-dione from *N*-methylmaleimide

Pelayo Camps,* Tània Gómez, and Ane Otermin

Laboratori de Química Farmacèutica (Unitat Associada al CSIC), Facultat de Farmàcia, and Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, Av. Joan XXIII 27-31, E-08028, Barcelona, Spain
E-mail: camps@ub.edu

Dedicated to Prof. Rosa M.ª Claramunt on the occasion of her 65th birthday

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.240

Abstract

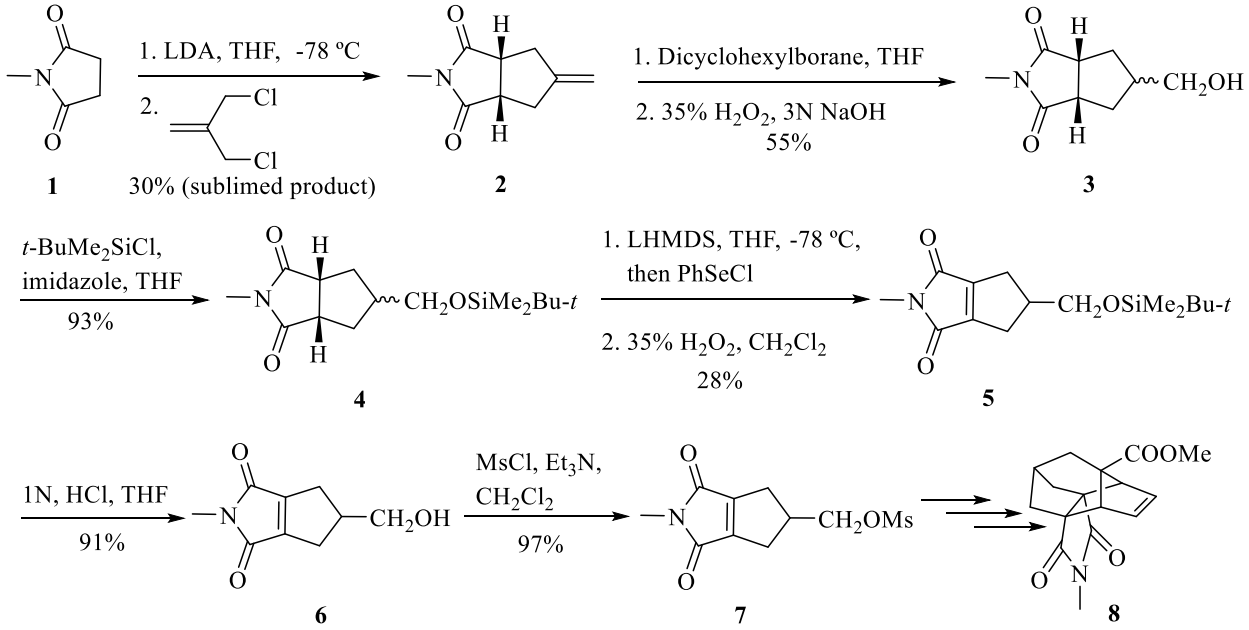
An improved preparation of 5-(*t*-butyldimethylsilyloxymethyl)-2-methyl-5,6-dihydrocyclopenta[*c*]pyrrole-1,3(2*H*,4*H*)-dione, a key intermediate for the preparation of the new polycyclic scaffold, methyl 2-methyl-1,3-dioxo-1,2,3,4,5,6,7,8-octahydro-3a,7,8-(epiprop[2]ene[1,1,3]triyl)-5,8a-methanocyclohepta[*c*]pyrrole-7-carboxylate, from *N*-methylmaleimide, is described.

Keywords: Diels-Alder reaction, methylenecyclopentane annulation, hydroboration, retro-Diels-Alder reaction

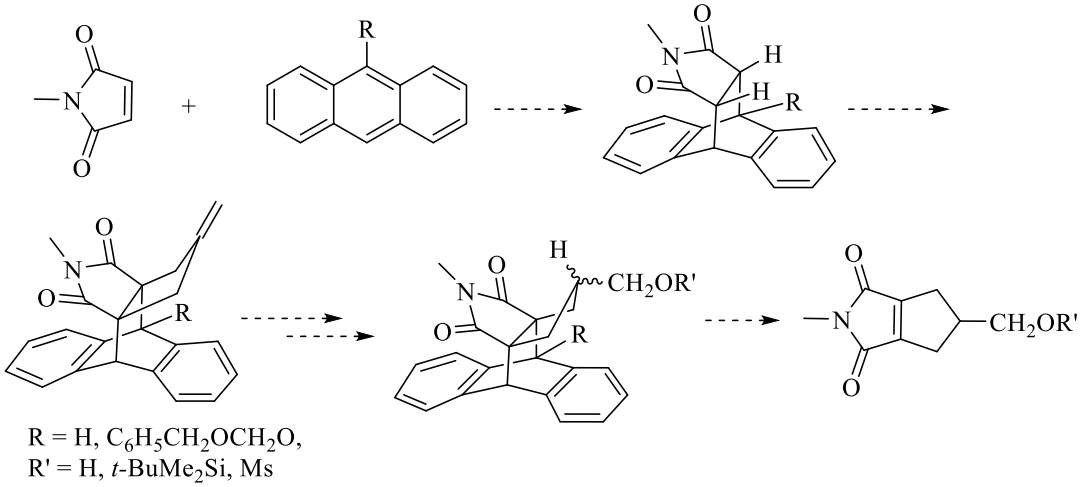
Introduction

We have recently described the preparation of the polycyclic compound **8**, as a new scaffold for the synthesis of compounds with potential biological activity.[1] However, the preparation of the key intermediate, alcohol **6** or derivatives, such as silyl ether **5** or mesylate **7**, implies several low yielding steps, resulting in difficult access to **8** in the required quantities for further transformations (Scheme 1). To solve this problem we planned an alternative approach to **5** or **6** which overcomes the low yielding conversion of the succinimide **4** to the maleimide **5**, by phenylselenylation followed by oxidative elimination. The starting compound would be *N*-methylmaleimide, in which the C=C bond would be protected as a Diels-Alder adduct with anthracene or a 9-substituted derivative as shown in Scheme 2. After annulation,

hydroboration/oxidation and, if necessary, protection, alcohol **5** or a protected derivative thereof might be obtained through a retro-Diels-Alder reaction.



Scheme 1. Described synthesis of silyl ether **5** and alcohol **6**, key intermediates for the preparation of polycycle **8**.

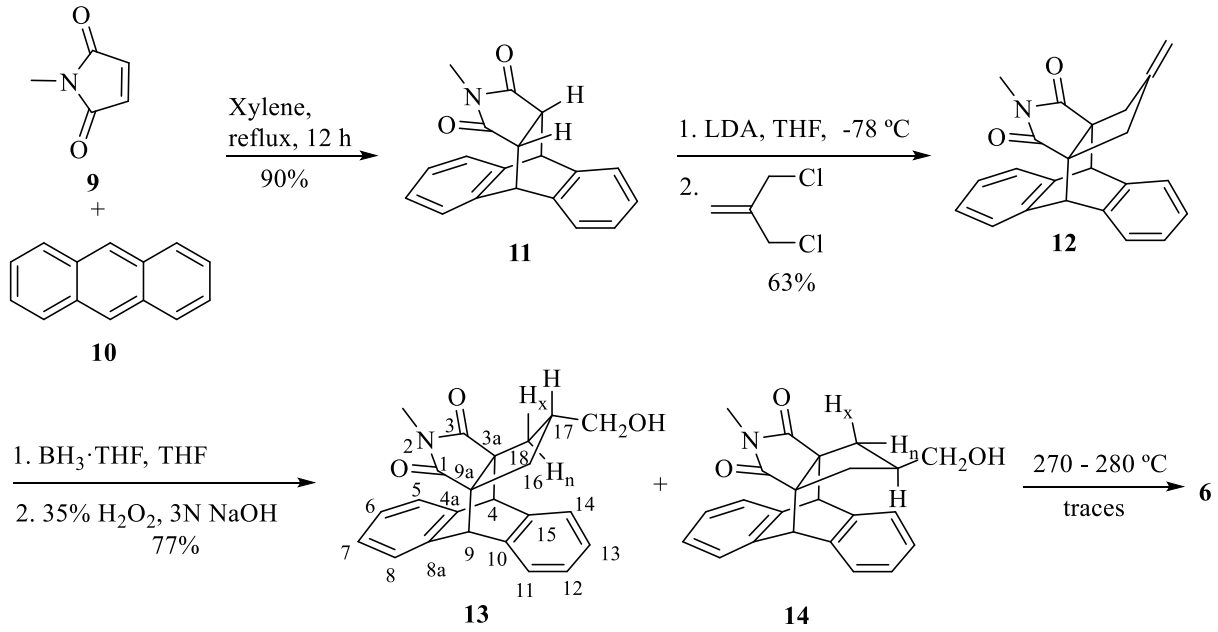


Scheme 2. Proposed alternative synthesis of alcohol **6** and derivatives.

Results and Discussion

As shown in Scheme 3, the known adduct **11**, derived from maleimide **9** and anthracene was prepared as described in 90% yield.[2,3] Annulation of **11** with 3-chloro-2-(chloromethyl)-1-propene under similar conditions to those used to prepare compound **2**, gave product **12** in 63% yield, much better than those obtained for **2** (30% of sublimed product).[4] Attempted hydroboration of **12** with 9-borabicyclo[3.3.1]nonane left the starting compound unchanged.[4,5] Probably, this reaction failed to take place by steric reasons since when this reaction was carried out by using the BH_3·THF complex, after oxidation with H_2O_2/NaOH, a stereoisomeric mixture of alcohols **13** and **14** in a ratio **13**/**14** about 2:1 (^{1}H NMR) was obtained in 77% yield. This mixture was not separated, since both stereoisomers would give the same products in the retro-Diels-Alder reaction. However, this stereoisomeric mixture as well as the rest of stereoisomeric mixtures prepared in this work were fully characterized by spectroscopic means, including ^{1}H/^{1}H homocorrelation (COSY and NOESY) and ^{1}H/^{13}C heterocorrelation spectra (gHSQC sequence for one bond correlations and gHMBC sequence for long range ones). In this way, the ^{1}H and ^{13}C NMR data of the main stereoisomer and most of the corresponding data of the minor stereoisomer of each mixture were obtained from the corresponding spectra as well as full assignment of the NMR data of the main stereoisomer of each mixture. Characterization of these mixtures was completed by HRMS, elemental analysis, IR and melting point.

The main stereoisomer of the above mixture seems to be **13**, derived from the hydroboration of **12** by the less hindered exo-face. The shown preferred conformation for **13** is based mainly on the ^{1}H NMR data for 16(18)-H_n, which appear quite shielded by the aromatic ring (δ 1.01 ppm) as a triplet ($^2J_{HH}$ = $^3J_{HH}$ = 13.0 Hz) due to the similar value of the geminal and vicinal (dihedral angle close to 180 º) coupling constants. The 16(18)-H_x do not show such kind of effect, appearing at δ 2.21 ppm. Also, in the NOESY spectrum, a small interaction is observed among 16(18)-H_n and 11(14)-H. For the minor stereoisomer (**14**) the 17-H is the more shielded proton (δ 1.20–1.30 ppm), suggesting the shown conformation to be the preferred one. In this case, 16(18)-H_n appear at δ 1.80 ppm and 16(18)-H_x at δ 1.90 ppm.



Scheme 3. Attempted synthesis of alcohol **6** from maleimide **9**.

Attempts to obtain alcohol **6**, by heating the mixture of alcohols **13** and **14** at 270–280 ºC in a sublimation equipment (cold finger) open to the atmosphere, were not satisfactory. Only traces of alcohol **6**, anthracene and most of the starting compounds were observed in the sublimed mixture. Also, the black not sublimed residue still contained the mixture of the starting compounds. Probably, these alcohols experience partly the desired retro-Diels-Alder reaction, sublimed and then condensed back to the mixture of starting alcohols. When a mixture of the *N*-ethyl analogs of **13** and **14** was heated in diphenyl ether at 250 ºC in the presence of dimethyl acetylenedicarboxylate or maleic anhydride, the starting mixture of alcohols was recovered unchanged.

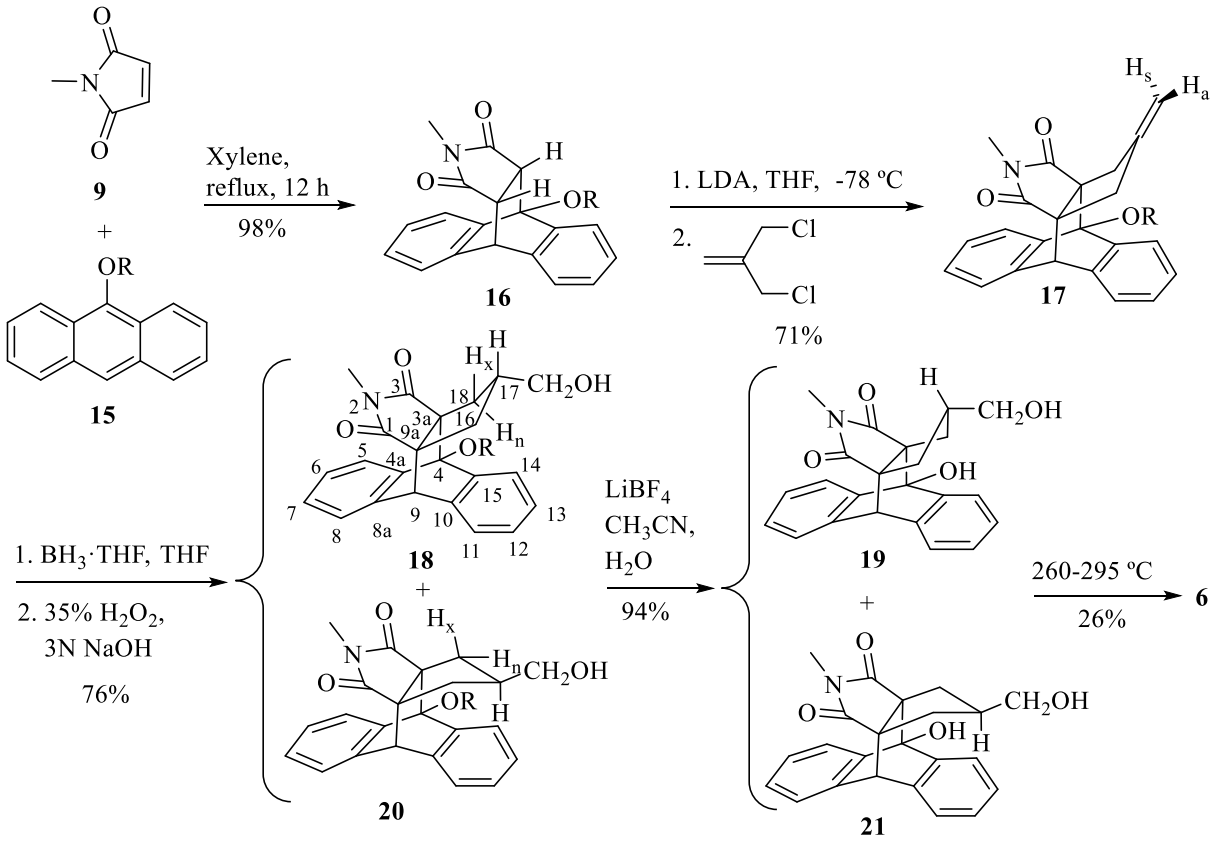
Retro-Diels-Alder reactions of anthracene adducts are usually carried out under flash vacuum pyrolysis (FVP) conditions, although there are several examples of reactions performed at 250–300 ºC.[5] Thus, the above result was not fully unexpected. Knapp et al.[6] had shown that the Diels-Alder adducts derived from 9-(benzyloxymethoxy)anthracene can easily experience the retro-Diels-Alder reaction by hydrolysis of the benzyloxymethoxy group and treatment of the resulting alcohol with potassium hydride in anhydrous 1,4-dioxane or THF at 25 ºC. Other authors have also carried out similar retro-Diels-Alder reactions.[7,8] Other pericyclic reactions have also been shown to be accelerated by this oxide anion effect.[9]

Consequently, we carried out the transformations shown in Scheme 4. Reaction of 9-(benzyloxymethoxy)anthracene (**15**) prepared as described,[7,9] with maleimide **9** gave the corresponding Diels-Alder adduct in 98% yield. Reaction of **16** with 3-chloro-2-(chloromethyl)-1-propene, as before for adduct **11**, gave product **17** in 71% yield. Hydroboration of **17** with the BH_3·THF complex followed by H_2O_2/NaOH oxidation gave a mixture of alcohols **18** and **20** in a ratio **18**/**20** about 2:1 (^{1}H NMR) in 76% yield. This mixture was not separated, since both stereoisomers after the retro-Diels-Alder reaction will give the same products. As before, the

main stereoisomer from this reaction seems to be **18** derived from the hydroboration of **17** by the less hindered exo-face. As before, the preferred conformation for **18** seems to be that shown on the basis of the ^{1}H NMR data. In this case, 16-H_n and 18-H_n are different but both appear quite shielded by the aromatic ring formed by the C10 to C15 atoms (16-H_n, δ 0.93 ppm, 18-H_n, δ 1.13 ppm) as triplets ($^2J_{HH}$ = $^3J_{HH}$ = 12.6 Hz) due to the equal value of the geminal and vicinal (dihedral angle close to 180 º) coupling constants. As expected, 16-H_x (δ 2.17 ppm), 18-H_x (δ 2.29 ppm) and 17-H (δ 1.85–1.97 ppm) are not similarly affected.

A long range ^{1}H/^{13}C heterocorrelation (gHMBC spectrum) between 9-H and C11 combined with the one bond ^{1}H/^{13}C homocorrelation (gHSQC spectrum) among C11 and 11-H, allowed to clearly assign 11-H. A small interaction in the NOESY spectrum among 16-H_n and 11-H, allowed us to assign 16-H_n. In a similar way were assigned 18-H_n and 14-H.

For the minor stereoisomer (**20**) the 17-H is the more shielded proton (δ 1.10–1.20 ppm), suggesting the shown conformation to be the preferred one. As expected, in this case, 16-H_n (δ 1.80 ppm), 18-H_n (δ 2.10 ppm), 16-H_x (δ 1.84–1.90 ppm) and 18-H_x (δ 1.84 ppm) appear not too much affected by the aromatic ring defined by the C10 to C15 atoms.

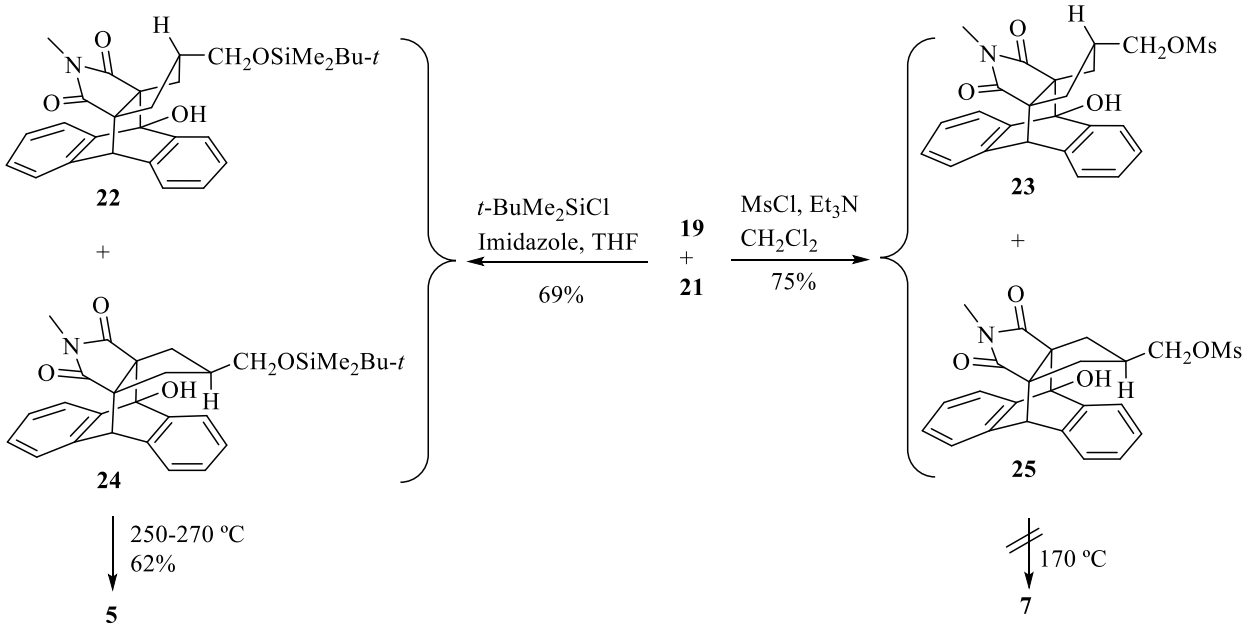


Scheme 4. Preparation of the mixture of diols **19** and **21** from maleimide **9** and anthracene derivative **15** and retro-Diels-Alder reaction of these diols to **6**.

Hydrolysis of the benzyloxymethoxy group of the **18**/**20** mixture to the **19**/**21** mixture was carried out in high yield by reaction with $LiBF_4$ in a mixture CH_3CN/H_2O at 90 ºC for 3 h, following a described procedure.[10,11] This procedure was preferred for the simplicity of the work-up to an alternative one which uses trifluoroacetic acid.[7,9]

As before, heating the mixture of diols **19**/**21** at 260−295 ºC (slightly over the melting point) for 3 days in a sublimation equipment (cold finger) open to the atmosphere, a mixture of anthrone, anthraquinone, a mixture of the starting diols **19** and **21** and the desired product **6** was obtained. Column chromatography of this mixture allowed us to separate a mixture of the less polar products anthrone and anthraquinone from a mixture of **6** and **19**+**21** in a ratio **6**/**19**+**21** close to 2:1 (^{1}H NMR), which correspond to about 26% yield of product **6**. The black residue of the sublimation still contained the starting mixture of alcohols. Apparently, as before, under the above conditions, the mixture of **19**+**21** experiences retro-Diels-Alder reaction, the formed products sublimed and the condensed products partly give back the starting compounds while anthrone is partly oxidized to anthaquinone by the air. Although this retro-Diels-Alder reaction led to **6**, the low yield of the process, the long reaction time in spite of the harsh conditions required with partial degradation of the starting products, led us to explore alternative transformations.

When the mixture of diols **19** and **21** was treated with KH or NaH in anh. THF, a precipitate was formed and, after the workup, the starting mixture of diols was recovered unchanged. This result might be due to precipitation of the potassium or sodium alkoxide derived from the deprotonation of the more acidic primary alcohol.



Scheme 5. Preparation of **5** by retro-Diels-Alder reaction from the mixture of silyl ethers **22** and **24** and degradation of the mixture of mesylates **23** and **25**.

Consequently, the mixture of diols **19** and **21** was chemoselectively protected at the primary alcohol as *t*-butyldimethylsilyl ether, to give the corresponding mixture of silyl ethers **22** and **24** in 69% yield. Treating this mixture with NaH or KH in THF at different temperatures and reaction times, always mixtures of starting compounds, anthrone and anthraquinone plus an acidic product, which lacks aromatic protons and has lost the symmetry of **5** (^{1}H NMR) was obtained. It might correspond to the product of hydrolysis of the imide function of **5**. The retro-Diels-Alder reaction of the anion of **22** or **24** generates the anthrone anion. Oxidation of this anion by the oxygen of the air would give anthraquinone plus hydroxide anion, which might be the responsible of the hydrolysis of the imide function of **5**. Also, some water might be present in the reaction medium, in spite of working under anhydrous conditions.

In view of these results, the mixture of silyl ethers **22** and **24** was heated at 250–270 ºC (over its melting point) in an sublimation equipment (cold finger) open to the atmosphere for 26 h to give a mixture, which on column chromatography gave pure **5** in 42% isolated yield (62% yield, taking into account the amount of recovered starting ethers). Taking into account the low expected volatility of the silyl ethers **22** and **24**, we consider that the products (anthrone and maleimide **5**) derived from the retrocycloaddition reaction of the starting compounds, once condensed, experience a Diels-Alder reaction reverting to the starting compounds. Fortunately, under the aerobic conditions used, most of the anthrone is oxidized to anthraquinone, unable to react with the desired maleimide **5**.

Taking into account the synthetic sequence given in Scheme 1, the possibility of obtaining mesylate **7** by retro-Diels-Alder reaction from the mixture of mesylates **23** and **25** was studied. Reaction of a mixture of diols **19** and **21** with a slight excess of mesyl chloride gave chemoselectively the corresponding mixture of mesylates **23** and **25** in 75% yield. However, when this mixture was heated at 170 ºC in a sublimation equipment (cold finger) open to the atmosphere, a fast degradation of the mesylates took place, no defined products being formed.

Conclusions

We have developed a synthetic sequence to prepare silyl ether **5** from *N*-methylmaleimide (**10**) which implies six steps with an overall yield of 21%, five times higher than that previously described,[1] starting from *N*-methylsuccinimide, that requires five steps with a global yield of 4.3%. The key points of the new procedure consists of: (1) protection of the C=C bond of the maleimide **9** as a Diels-Alder adduct with 9-benzyloxymetoxyanthracene, (ii) a thermal retro-Diels-Alder reaction of the mixture of silyl ethers **22** and **24** to regenerate the C=C bond of the maleimide, and (iii) although the hydroboration/oxidation of **27** gives a stereoisomeric mixture

of alcohols, it is not necessary to separate this mixture, since both stereoisomers gave the same product at the end of the synthetic sequence.

Experimental Section

General. Melting points were determined in open capillary tubes with a MFB 595010 M Gallenkamp melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (400 MHz, 100.6 MHz for ^{13}C) spectrometer. Chemical shifts (δ) are reported in ppm related to internal TMS or $CDCl_3$. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad or their combinations. Assignments given for the NMR spectra are based on DEPT, COSY, NOESY, ^{1}H/^{13}C single quantum correlation (gHSQC sequence) and ^{1}H/^{13}C multiple bond correlation (gHMBC sequence) spectra. IR spectra were registered on a FTIR Perkin–Elmer Spectrum RX1 spectrometer using the Attenuated Total Reflectance (ATR) Technique. Absorption values are given as wavenumbers (cm^{-1}), the intensity of the absorptions are given as strong (s), medium (m) or weak (w). High-resolution mass spectra (HRMS) were carried out at the Mass Spectrometry Unity of the *Centres Científics i Tecnològics de la Universitat de Barcelona* (CCiTUB) on a LC/MSD-TOF spectrometer with electrospray ionization (ESI-TOF-MS) from Agilent Technologies and are reported as *m*/*z* (relative ratio). The elemental analyses were carried out in Thermofinnigan elemental microanalyzers: (A5) Flash 1112 series model for the C, H and N determinations and (A7) Flash 2000 series model for the C, H, N and S determinations, at the IIQAB (CSIC) of Barcelona, Spain. For the flash column chromatography, silica gel 60 AC (35–70 μM, SDS, ref. 2000027) was used. The eluents employed are reported as volume/volume percentages. Thin-layer chromatography (TLC) was performed on aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref. 1.05554) and spots were visualized with UV light, a 1% aqueous solution of $KMnO_4$. Anthrone was purchased from Alfa Aesar, *N*-methylmaleimide and *t*-butyldimethylsilyl chloride from TCI, anthracene from Merck, benzyloxymethyl chloride and $LiBF_4$ from Sigma Aldrich, 3-chloro-2-(chloromethyl)-1-propene from Secant Chemical Inc., all of them were used without further purification.

(3a*R*,9a*S*)-2-Methyl-17-methylene-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1*H*-benz-[*f*]isoindole-1,3(2*H*)-dione (12). To a cold (−78 ºC, acetone/solid CO_2) and magnetically stirred solution of diisopropylamine (0.8 mL, 5.7 mmol) in anhydrous THF (15 mL) under an argon atmosphere, a solution of *n*-BuLi in hexanes (2.3 mL, 2.5 M, 5.7 mmol) was added dropwise. When *n*-BuLi addition was finished, the solution was allowed to warm to 0 ºC for 1 h, it was cooled again to −78 ºC, and a solution of **11** (690 mg, 2.38 mmol) in anhydrous THF (8 mL) was added dropwise. Then, the solution was stirred a −78 ºC for 15 min and allowed to warm to 0 ºC for 1 h. The solution was again cooled to −78 ºC and 3-chloro-2-(chloromethyl)-1-propene (0.36 mL 96% content, 373 mg, 3.0 mmol) was added dropwise. The reaction mixture was allowed to

warm to room temperature and it was stirred for 3 days at this temperature. The mixture was made acidic with aqueous 1N HCl (10 mL) and was extracted with Et_2O (3×50 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a brown waxy residue (960 mg) that was subjected to column chromatography (silica gel 35–70 μm, 30 g, hexane/EtOAc mixtures) to give on elution with hexane/EtOAc 9:1, product **12** (515 mg, 63% yield) as a yellow solid. R_f 0.51 (silica gel, 8 cm, hexane/EtOAc 8:2); mp 190–192 ºC (from EtOAc/hexane); IR (ATR, ν_{max}, cm^{-1}): 1770w and 1693s (C=O st); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (br s, H_2O), 2.11 [dt, $^2J_{HH}$ 16.4 Hz, $^4J_{HH}$ 2.4 Hz, 2H, 16(18)-H_n], 2.47 (s, 3H, *N*-C*H*$_3$), 2.64 [br d, $^2J_{HH}$ 16.4 Hz, 2H, 16(18)-H_x], 4.51 [s, 2H, 4(9)-H], 4.61–4.62 (br s, 2H, C17=C*H*$_2$), 7.06–7.10 [m, 2H, 6(7)-H], 7.17–7.20 [m, 2H, 12(13)-H], 7.21–7.25 [m, 2H, 5(8)-H], 7.34–7.38 [m, 2H, 11(14)-H]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.5 (CH_3, *N*-*C*H_3), 39.3 [CH_2, C16(18)], 49.5 [CH, C4(9)], 62.0 [C, C3a(9a)], 108.8 (CH_2, C17=*C*H_2), 124.9 [CH, C5(8)], 126.6 [CH, C11(14)], 126.81 [CH, C12(13)], 126.85 [CH, C6(7)], 139.6 [C, C4a(8a)], 139.9 [C, C10(15)], 146.6 (C, C17), 180.1 [C, C1(3)]; HRMS (ESI-TOF): calcd. for $[C_{23}H_{19}NO_2+H]^+$: 342.1489. Found: 342.1485; Anal. calcd. for $C_{23}H_{19}NO_2 \cdot 0.25H_2O$: C, 79.86; H, 5.68; N, 4.05%. Found: C, 79.47; H, 5.62; N, 3.88%.

(3a*R*,9a*S*,17*r*)-17-(Hydroxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (13) and (3a*R*,9a*S*,17*s*)-17-(hydroxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (14). To a cold (0 ºC, ice-water bath) and magnetically stirred solution of compound **12** (340 mg, 1.00 mmol) in anhydrous THF (12 mL) under an argon atmosphere, a solution of the BH_3·THF complex in anhydrous THF (2.3 mL, 1M en THF, 2.3 mmol) was added dropwise and the reaction mixture was stirred at 0 ºC for 4 h. After addition of EtOH (1.1 mL), the mixture was allowed to warm to room temperature, and aqueous solutions of 35% H_2O_2 (0.81 mL) and 3 M NaOH (1.3 mL) were simultaneously added dropwise in 5 min, occasionally cooling with a water bath, and the reaction mixture was stirred at room temperature for 15 min. Water (6 mL) and EtOAc (12 mL) were added, the organic phase was separated and the aqueous one was extracted with EtOAc (2×12 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and concentrated to dryness in vacuo to give a white solid (450 mg) that was subjected to column chromatography (silica gel 35–70 μm, 13.5 g, hexane/EtOAc mixtures). On elution with hexane/EtOAc from 3:2 to 1:1, a stereoisomeric mixture of alcohols **13** and **14** in an approximate ratio **13**/**14** 2:1 (^{1}H NMR) (276 mg, 77% yield) was isolated as a white solid.

Analytical and spectroscopic data of the mixture of 13 and 14: R_f 0.61 (silica gel, 10 cm, hexane/EtOAc 4:1); mp 236–238 ºC; IR (ATR, ν_{max}, cm^{-1}): 3600–3200 [max. at 3361w, O–H st], 1768w and 1696s (C=O st). HRMS (ESI-TOF): calcd. for $[C_{23}H_{21}NO_3+H]^+$: 360.1594. Found: 360.1591; Anal. calcd. for $C_{23}H_{21}NO_3 \cdot 0.5H_2O$: C, 74.98; H, 6.02; N, 3.80%. Found: C, 75.23; H, 6.29; N, 3.41%.

NMR data of 13 from the spectra of the mixture 13/14 (ratio 13/14~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 [t, $^2J_{HH}$ = $^3J_{HH}$ 13.0 Hz, 2H, 16(18)-H_n], 1.2–1.4 (br s, 1H, OH), 1.87–1.99 (m + br s, 2H, 17-H and H_2O), 2.21 [dd, $^2J_{HH}$ 13.4 Hz, $^3J_{HH}$ 6.2 Hz, 2H, 16(18)-H_x], 2.48 (s, 3H,

N-C*H*$_3$), 3.22 (d, $^3J_{HH}$ 6.4 Hz, 2H, C*H*$_2$OH), 4.47 [s, 2H, 4(9)-H], 7.05–7.08 [m, 2H, 6(7)-H], 7.17–7.20 [m, 2H, 12(13)-H], 7.19–7.22 [m, 2H, 5(8)-H], 7.33–7.38 [m, 2H, 11(14)-H]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.6 (CH_2, *N*-*C*H$_3$), 35.3 [CH_2, C16(18)], 42.3 (CH, C17), 49.4 [CH, C4(9)], 62.7 [C, C3a(9a)], 64.9 (CH_2, CH_2OH), 124.9 [CH, C5(8)], 126.6 [CH, C11(14)], 126.7 [CH, C6(7)], 126.77 [CH, C12(13)], 139.7 [C, C4a(8a)], 140.07 [C, C10(15)], 180.5 [C, C1(3)].

Significant NMR data of 14 from the spectra of the mixture 13/14 (ratio 13/14~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.30 (m, 1H, 17-H), 1.80 [dd, $^2J_{HH}$ 14.6 Hz, $^3J_{HH}$ 7.8 Hz, 2H, 16(18)-H$_n$], 1.90 [dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 6.4 Hz, 2H, 16(18)-H$_x$], 2.43 (s, 3H, *N*-C*H*$_3$), 3.20 (d, $^3J_{HH}$ 6.4 Hz, 2H, C*H*$_2$OH), 4.50 [s, 2H, 4(9)-H]; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.4 (CH_2, *N*-*C*H$_3$), 35.4 [CH_2, C16(18)], 43.4 (CH, C17), 50.7 [CH, C4(9)], 63.3 [C, C3a(9a)], 65.4 (CH_2, CH_2OH), 124.8 [CH, C5(8)], 126.1 [CH, C11(14)], 126.77 [CH, C6(7)], 126.82 [CH, C12(13)], 139.7 [C, C4a(8a)], 140.11 [C, C10(15)], 180.5 [C, C1(3)].

(3a*R,9a*R**)-4-[(Benzyloxy)methoxy)-2-methyl-3a,4,9,9a-tetrahydro-4,9[1',2']benzeno-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (16).** A magnetically stirred solution of *N*-methylmaleimide (**9**) (1.00 g, 9.00 mmol) and 9-[(benzyloxy)methoxy]anthracene **15** (2.83 g, 9.00 mmol) in xylene (140 mL) was heated at 140 ºC for 12 h. The solution was allowed to cool to room temperature with formation of a white precipitate, that was filtered in vacuo and washed with cold MeOH (15 mL) to give a white solid (3.88 g) that was heated with hexane (160 mL) to give product **16** (3.75 g, 98% yield) as a white solid. R_f 0.27 (silica gel, 9 cm, hexane/EtOAc 85:15); mp 129–131 ºC (xylene); IR (ATR, ν_{max}, cm^{-1}): 1693s (C=O st). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H, *N*-C*H*$_3$), 3.32 (dd, $^3J_{HH}$ 8.6 Hz, $^3J_{HH}$ 3.0 Hz, 1H, 9a-H), 3.47 (d, $^3J_{HH}$ 8.8 Hz, 1H, 3a-H), 4.71 (d, $^3J_{HH}$ 3.2 Hz, 1H, 9-H), 5.06 (d, $^2J_{HH}$ 11.8 Hz, 1H) and 5.21 (d, $^2J_{HH}$ 11.8 Hz, 1H) (OC*H*$_2$Ph), 5.64 (d, $^2J_{HH}$ 5.6 Hz, 1H) and 5.72 (d, $^2J_{HH}$ 6.0 Hz, 1H) (OC*H*$_2$O), 7.14 (dt, $^4J_{HH}$ 1.2 Hz, $^3J_{HH}$ 7.4 Hz, 1H, 7-H), 7.17–7.26 [complex signal, 4H, 6-H, 8-H, 12-H and 13-H), 7.32–7.37 (tm, $^3J_{HH}$ 7.4 Hz, 1H, Ph-4-H), 7.38–7.44 (complex signal, 3H, Ph-3(6)-H and 11-H], 7.53–7.55 [dm, $^3J_{HH}$ 7.2 Hz, 2H, Ph-2(6)-H], 7.65–7.68 (dm, $^3J_{HH}$ 7.6 Hz, 1H, 5-H), 7.72–7.75 (dm, $^3J_{HH}$ 6.8 Hz, 1H, 14-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.3 (CH_3, *N*-*C*H$_3$), 44.6 (CH, C9), 47.4 (CH, C3a), 47.9 (CH, C9a), 71.4 (CH_2, *C*H$_2$C$_6$H$_5$), 81.8 (C, C4), 92.0 (CH_2, OCH_2O), 121.8 (CH, C5), 122.3 (CH, C14), 124.0 (CH, C11), 124.4 (CH, C8), 126.6 (CH, C13), 126.9 (CH, C12), 127.01 (CH, C7), 127.04 (CH, C6), 127.8 (Ph-C4), 128.2 [Ph-C2(6], 128.5 [Ph-C3(5)], 136.3 (C, C8a), 137.9 (C, Ph-C1), 139.7 (C, C4a), 140.3 (C, C10), 141.5 (C, C15), 174.1 (C, C1), 176.2 (C, C3). HRMS (ESI-TOF): calcd. for [$C_{27}H_{23}NO_4$+Na]$^+$: 448.1519. Found: 448.1513; Anal. calcd. for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29%. Found: C, 76.08; H, 5.55; N, 3.24%.

(3a*R,9a*R**)-4-[(Benzyloxy)methoxy]-2-methyl-17-methylene-4,9-dihydro-4,9[1',2']benzene-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (17).** To a cold (–78 ºC, acetone/solid CO_2 bath) and magnetically stirred solution of diisopropylamine (1.3 mL, 9.3 mmol) in anhydrous THF (25 mL) under an argon atmosphere, a solution of *n*-BuLi in hexanes (3.7 mL, 2.5 M, 9.2 mmol) was added dropwise. When *n*-BuLi addition was finished, the solution was allowed to warm to 0 ºC for 1 h, it was cooled again to –78 ºC, and a solution of **16** (1.65 g, 3.88 mmol) in

anhydrous THF (20 mL) was added dropwise. Then, the solution was stirred a −78 ºC for 15 min and allowed to warm to 0 ºC for 1 h. The solution was again cooled to −78 ºC and 3-chloro-2-(chloromethyl)-1-propene (0.56 mL 96% content, 580 mg, 4.6 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and it was stirred for 3 days at this temperature. The mixture was made acidic with aqueous 2N HCl (6 mL) and was extracted with Et_2O (3×50 mL). The combined organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a brown waxy residue (1.90 g) that was subjected to column chromatography (silica gel 35–70 μm, 57 g, hexane/EtOAc mixtures) to give on elution with hexane/EtOAc 9:1, product **17** (1.32 g, 71% yield) as a yellow solid. R_f 0.33 (silica gel, 9 cm, hexane/EtOAc 4:1); mp 62.5–65 ºC (EtOAc/hexane); IR (ATR, ν_{max}, cm^{-1}): 1772w and 1697s (C=O st). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01–2.04 (dm, $^2J_{HH}$ 15.4 Hz, 1H, 16-H_n), 2.26–2.31 (dm, $^2J_{HH}$ 15.6 Hz, 1H, 18-H_n), 2.46 (s, 3H, *N*-CH_3), 2.60 (br d, $^2J_{HH}$ 15.4 Hz, 1H, 16-H_x), 2.69 (d ancho, $^2J_{HH}$ 15.6 Hz, 1H, 18-H_x), 4.45 (s, 1H, 9-H), 4.59–4.61 (br s, 1H, 17=CH_a), 4.61–4.63 (br s, 1H, 17=CH_s), 5.06 (d, $^2J_{HH}$ 11.8 Hz, 1H) and 5.17 (d, $^2J_{HH}$ 11.8 Hz, 1H) (OCH_2Ph), 5.50 (s, 2H, OCH_2O), 7.13 (overlapped dt, $^4J_{HH}$ 1.2 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 7-H), 7.17 (overlapped dt, $^4J_{HH}$ 1.6 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 6-H), 7.21–7.28 [complex signal, 3H, 8-H, 12-H, 13-H), 7.33–7.39 (complex signal, 2H, Ph-4-H and 11-H), 7.40–7.45 [tm, $^3J_{HH}$ 7.2 Hz, 2H, Ph-3(5)-H], 7.54–7.57 [dm, $^3J_{HH}$ 7.2 Hz, 2H, Ph-2(6)-H], 7.76–7.78 (dm, $^3J_{HH}$ 7.2 Hz, 1H, 5-H), 7.79–7.82 (dm, $^3J_{HH}$ 6.8 Hz, 1H, 14-H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.6 (CH_3, *N*-CH_3), 38.3 (CH_2, C18), 39.0 (CH_2, C16), 48.7 (CH, C9), 64.0 (C, C3a), 64.8 (C, C9a), 70.5 (CH_2, C$H_2C_6H_5$), 87.1 (C, C4), 92.1 (CH_2, OCH_2O), 108.9 (CH_2, 17=CH_2), 122.7 (CH, C5), 124.4 (CH, C14), 124.8 (CH, C8), 126.3 (CH, C11), 126.9 (CH, C13), 127.0 (CH, C6), 127.2 (2CH, C7 and C12), 127.8 (CH, Ph-C4), 128.3 [CH, Ph-C2(6)], 128.5 [CH, Ph-C3(5)], 137.8 (C, Ph-C1), 138.16 (C, C8a), 138.22 (C, C10), 139.5 (C, C4a), 139.8 (C, C15), 146.6 (C, C17), 177.2 (C, C3), 179.4 (C, C1). HRMS (ESI-TOF): calcd. for $[C_{31}H_{27}NO_4+NH_4]^+$: 495.2278. Found: 495.2273; Anal. Calcd. for $C_{31}H_{27}NO_4$: C, 77.97; H, 5.70; N, 2.93%. Found: C, 77.56; H, 5.84; N, 2.63%.

(3a*R,9a*R**,17*S**)-4-(Benzyloxymethoxy)-17-(hydroxymethyl)-2-methyl-4,9-dihydro-4,9-[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (18) and (3a*R**, 9a*R**, 17*R**)-4-(benzyloxymethoxy)-17-(hydroxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (20).** To a cold (0 ºC, ice-water bath) and magnetically stirred solution of compound **17** (1.00 g, 2.09 mmol) in anhydrous THF (26 mL) under an argon atmosphere, a solution of the BH_3·THF complex in anhydrous THF (4.8 mL, 1 M en THF, 4.8 mmol) was added dropwise and the reaction mixture was stirred at 0 ºC for 4 h. After addition of EtOH (2.3 mL), the mixture was allowed to warm to room temperature, and aqueous solutions of 35% H_2O_2 (1.7 mL) and 3 M NaOH (2.7 mL) were simultaneously added dropwise in 5 min, occasionally cooling with a water bath, and the reaction mixture was stirred at room temperature for 15 min. Water (12 mL) and EtOAc (25 mL) were added, the organic phase was separated and the aqueous one was extracted with EtOAc (2×25 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and concentrated to dryness in vacuo to give a white solid (1.29 g) that was subjected to column chromatography (silica gel 35–70 μm, 40 g,

hexane/EtOAc mixtures). On elution with hexane/EtOAc 1:1, a stereoisomeric mixture of alcohols **18** and **20** in an approximate ratio **18**/**20** 2:1 (^{1}H NMR) (790 mg, 76% yield) was isolated as a white solid.

Analytical and spectroscopic data of the mixture of 18 and 20: R_f 0.48 (silica gel, 8 cm, hexane/EtOAc 2:8); mp 86–89 ºC (EtOAc/hexane); IR (ATR, ν_{max}, cm^{-1}): 3480w (O–H st), 1770w and 1694s (C=O st). HRMS (ESI-TOF): calcd. for $[C_{31}H_{29}NO_5+H]^+$: 496.2118. Found: 496.2111; Anal. calcd. for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83%. Found: C, 75.07; H, 6.05; N, 2.65%.

NMR data of 18 from the spectra of the mixture 18/20 (ratio 18/20~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.93 (t, $^2J_{HH}$ 12.6 Hz, 1H, 16-H$_n$), 1.0–1.6 (br s, OH), 1.13 (t, $^2J_{HH}$ 12.6 Hz, 1H, 18-H$_n$), 1.85–1.97 (m, 1H, 17-H), 2.17 (ddd, $^2J_{HH}$ 13.0 Hz, $^3J_{HH}$ 6.0 Hz, $^4J_{HH}$ 1.4 Hz, 1H, 16-H$_x$), 2.29 (ddd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 6.0 Hz, $^4J_{HH}$ 1.2 Hz, 1H, 18-H$_x$), 2.48 (s, 3H, *N*-CH$_3$), 3.21 (overlapped dd, $^3J_{HH}$ 6.0 Hz, 1H, C*H$_a$*OH), 3.23 (dd, $^2J_{HH}$ 10.6 Hz, $^3J_{HH}$ 6.2 Hz, 1H, C*H$_b$*OH), 4.41 (s, 1H, 9-H), 5.04 (d, $^2J_{HH}$ 12.0 Hz, 1H, C*H$_a$*C$_6$H$_5$), 5.15 (d, $^2J_{HH}$ 12.0 Hz, 1H, C*H$_b$*C$_6$H$_5$), 5.49 (s, 2H, OCH$_2$O), 7.10–7.18 (complex signal, 2H, 6-H and 7-H), 7.21–7.30 (complex signal, 3H, 8-H, 12-H and 13-H), 7.32–7.37 (overlapped tm, $^3J_{HH}$ 7.6 Hz, 1H, Ar-4-H), 7.36–7.39 (m, 1H, 11-H), 7.39–7.44 [m, Ar-3(5)-H], 7.53–7.56 [dm, $^3J_{HH}$ 8,4 Hz, 2H, Ar-2(6)-H], 7.72–7.74 (dm, $^3J_{HH}$ 7.2 Hz, 1H, 5-H), 7.79–7.82 (dm, $^3J_{HH}$ 7.2 Hz, 1H, 14-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.6 (CH$_3$, *N*-*C*H$_3$), 34.5 (CH$_2$, C18), 35.0 (CH$_2$, C16), 42.5 (CH, C17), 48.6 (CH, C9), 64.9 (C, C9a), 65.5 (CH$_2$, CH$_2$OH), 66.5 (C, C3a), 70.5 (CH$_2$, *C*H$_2$C$_6$H$_5$), 87.0 (C, C4), 92.0 (CH$_2$, OCH$_2$O), 122.7 (CH, C5), 124.3 (CH, C14), 124.7 (CH, C8), 126.4 (CH, C11), 126.7 (CH, C13), 126.9 (CH, C6), 127.1 (2CH, C7 and C12), 127.8 (CH, Ar-C4), 128.3 [CH, Ar-C2(6)], 128.5 [CH, Ar-C3(5)], 137.8 (C, Ar-C1), 138.3 (C, C8a), 138.4 (C, C10), 139.7 (C, C4a), 139.9 (C, C15), 177.5 (C, C3), 179.68 (C, C1).

Significant NMR data of 20 from the spectra of the mixture 18/20 (ratio 18/20~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.20 (m, 1 H, 17-H), 1.71 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 8.0 Hz, 1H, 16-H$_n$), 1.84 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 6.8 Hz, 1H, 18-H$_x$), 1.84–1.90 (overlapped dd, $^3J_{HH}$ 6.4 Hz, 1H, 16-H$_x$), 2.10 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 8.4 Hz, 1H, 18-H$_n$), 2.42 (s, 3H, *N*-CH$_3$), 3.17 (dd, $^2J_{HH}$ 10.6 Hz, $^3J_{HH}$ 6.2 Hz, 1H) and 3.19 (dd, $^2J_{HH}$ 10.6 Hz, $^3J_{HH}$ 6.0 Hz, 1H) (CH$_2$OH), 4.44 (s, 1H, 9-H), 5.06 (d, $^2J_{HH}$ 11.6 Hz, 1H, C*H$_a$*C$_6$H$_5$), 5.15 (d, $^2J_{HH}$ 11.6 Hz, 1H, C*H$_b$*C$_6$H$_5$), 5.47 (d, $^2J_{HH}$ 6.0 Hz, 1H, OC*H$_a$*O), 5.49 (d, $^2J_{HH}$ 6.0 Hz, 1H, OC*H$_b$*O). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.5 (CH$_3$, *N*-*C*H$_3$), 33.0 (CH$_2$, C18), 35.2 (CH$_2$, C16), 43.4 (CH, C17), 49.9 (CH, C9), 65.0 (C, C9a), 65.6 (CH$_2$, CH$_2$OH), 66.5 (C, C3a), 70.4 (CH$_2$, *C*H$_2$C$_6$H$_5$), 87.6 (C, C4), 92.2 (CH$_2$, OCH$_2$O), 177.6 (C, C3), 179.74 (C, C1).

(3a*R,9a*R**,17*S**)-4-Hydroxy-17-(hydroxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (19) and (3a*R**,9a*R**,17*R**)-4-hydroxy-17-(hydroxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]-isoindole-1,3(2*H*)-dione (21).** $LiBF_4$ (460 mg, 4.90 mmol) was added to a mixture of water (0.6 mL) and acetonitrile (14.4 mL) and the mixture was stirred for 10 min at room temperature till complete solution of the solid. Then, a mixture of **18** and **20** (ratio **18**/**20** close to 2:1) (405 mg,

0.82 mmol) was added and the reaction mixture was heated to 90 ºC for 3 h. The solution was allowed to cool to room temperature, was diluted with CH_2Cl_2 (35 mL) and was washed with H_2O (10 mL), saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (14 mL). The organic phase was dried (anhydrous Na_2SO_4) and concentrated in vacuo to dryness to give a residue (355 mg) that was subjected to column chromatography (silica gel 35–70 µm, 14 g, hexane/EtOAc mixtures). On elution with hexane/EtOAc 3:2, a stereoisomeric mixture of **19** and **21** (ratio **19**/**21** about 2:1) (287 mg, 94% yield) was obtained as a white solid.

Analytical and spectroscopic data of the mixture of 19 and 21: R_f 0.41 (silica gel, 9 cm, hexane/EtOAc 2:8); mp 262.5–264 ºC (EtOAc/hexane); IR (ATR, ν_{max}, cm^{-1}): 3600–3150 (max. at 3500w, O–H st), 1767w and 1686s (C=O st); HRMS (ESI-TOF): calcd. for $[C_{23}H_{21}NO_4+H]^+$: 376.1543. Found: 376.1538: Anal. calcd. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73%. Found: C, 73.26; H, 5.80; N, 3.52%.

NMR data of 19 from the spectra of the mixture 19/21 (ratio 19/21~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.1–1.5 (br s, 1H CH_2O*H*), 1.06 (t, $^2J_{HH}$ = $^3J_{HH}$ 12.8 Hz, 1H, 16-H_n), 1.15 (t, $^2J_{HH}$ = $^3J_{HH}$ 13.0 Hz, 1H, 18-H_n), 1.90–2.02 (m, 1H, 17-H), 2.19 (dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 6.0 Hz, 1H, 18-H_x), 2.24 (dd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 6.0 Hz, 1H, 16-H_x), 2.49 (s, 3H, *N*-CH_3), 3.19–3.27 (m, 2H, CH_2O), 4.19 (br s, 1H, OH), 4.42 (s, 1H, 9-H), 7.09 (t, $^3J_{HH}$ 7.2 Hz, 1H, 7-H), 7.17 (overlapped t, $^3J_{HH}$ 6.8 Hz, 1H, 6-H), 7.18–7.23 (complex signal, 2H, 8-H and 12-H), 7.26–7.31 (m, 1H, 13-H), 7.34 (d, $^3J_{HH}$ 7.2 Hz, 1H, 11-H), 7.42 (d, $^3J_{HH}$ 7.6 Hz, 1H, 5-H), 7.68 (d, $^3J_{HH}$ 7.6 Hz, 1H, 14-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.6 (CH_3, *N*-*C*H_3), 33.4 (CH_2, C18), 35.5 (CH_2, C16), 42.3 (CH, C17), 48.1 (CH, C9), 63.8 (C, C9a), 64.1 (C, C3a), 64.9 (CH_2, CH_2O), 79.6 (C, C4), 120.90 (CH, C5), 123.0 (CH, C14), 124.4 (CH, C8), 126.0 (CH, C11), 126.8 (2CH, C6 and C12), 127.0 (2CH, C7 and C13), 137.79 (C, C10), 138.0 (C, C8a), 140.5 (C, C15), 141.7 (C, C4a), 180.11 (C, C1), 181.5 (C, C3).

Significant NMR data of 21 from the spectra of the mixture 19/21 (ratio 19/21~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06–1.27 (m, 1 H, 17-H), 1.74 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 6.8 Hz, 1H, 18-H_n), 1.84 (dd, $^2J_{HH}$ 14.0 Hz, $^3J_{HH}$ 8.0 Hz, 1H, 16-H_n), 1.92–1.98 (overlapped dd, 1H, 16-H_x), 2.12 (dd, $^2J_{HH}$ 14.0 Hz, $^3J_{HH}$ 8.0 Hz, 1H, 18-H_x), 2.44 (s, 3H, *N*-CH_3), 3.19–3.27 (m, 2H, CH_2OH), 4.22 (br s, 1H, OH), 4.44 (s, 1H, 9-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.4 (CH_3, *N*-*C*H_3), 32.3 (CH_2, C18), 35.8 (CH_2, C16), 43.4 (CH, C17), 49.3 (CH, C9), 64.4 (C, C9a), 65.0 (C, C3a), 65.4 (CH_2, CH_2O), 79.3 (C, C4), 120.87 (CH, C5), 122.6 (CH, C14), 124.3 (CH, C8), 125.4 (CH, C11), 126.7 (2CH, C8 and C12), 126.8 (2CH, C7 and C13), 137.83 (C, C10), 138.1 (C, C8a), 140.6 (C, C15), 141.4 (C, C4a), 180.09 (C, C1), 181.3 (C, C3).

(3a*R,9a*R**,17*S**)-17-(*t*-Butyldimethylsilyloxymethyl)-4-hydroxy-2-methyl-4,9-dihydro-4,9-[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (22) and (3a*R**,9a*R**,17*R**)-17-(*t*-Butyldimethylsilyloxymethyl)-4-hydroxy-2-methyl-4,9-dihydro-4,9[1',2']-benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (24).** To a solution of a mixture of diols **19** and **21** (560 mg, 1.49 mmol) in anhydrous THF (12 mL) under an argon atmosphere, imidazole (241 mg, 3.54 mmol) was added and the mixture was stirred for 10 min at room temperature. *t*-Butyldimethylsilyl chloride (271 mg, 1.76 mmol) was added and the mixture was

stirred at room temperature for 18 h. The formed suspension was filtered through a pad of silica gel and Celite® to remove the imidazolium chloride. The solid was washed with EtOAc (15 mL) and the combined filtrate and washings were concentrated in vacuo to dryness. The residue was taken in EtOAc (10 mL), washed with water (3×5 mL) and brine (2×5 mL). The organic phase was dried (anhydrous Na_2SO_4) and concentrated to dryness in vacuo to give a yellow solid (755 mg), that was subjected to column chromatography (silica gel, 35–70 μm, 30 g, hexane/EtOAc mixtures) to give on elution with hexane/EtOAc 95:5, a mixture of silyl ethers **22** and **24** in a ratio **22**/**24** about 2:1 (501 mg, 69% yield) as a white solid.

Analytical and spectroscopic data of the mixture of 22 and 24: R_f 0.35 (silica gel, 9 cm, hexane/EtOAc 4:1); mp 125–127 ºC (AcOEt/hexane); IR (ATR, ν_{max}, cm^{-1}): 3530w (O–H st), 1769w, 1688s and 1682s (C=O st). HRMS (ESI-TOF): calcd. for $[C_{29}H_{35}NO_4Si+H]^+$: 490.2408. Found: 490.2411. Anal. calcd. for $C_{29}H_{35}NO_4Si$: C, 71.13; H, 7.20; N, 2.86%. Found: C, 71.04; H, 7.32; N, 2.68%.

NMR data of 22 from the spectra of the mixture 22/24 (ratio 22/24~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ –0,12 [s, 6H, $Si(CH_3)_2$], 0.76 [s, 9H, $C(CH_3)_3$], 1.17 (t, $^2J_{HH}$ = $^3J_{HH}$ 12.6 Hz, 1H, 16-H_n), 1.26 (t, $^2J_{HH}$ = $^3J_{HH}$ 12.8 Hz, 1H, 18-H_n), 1.81–1.92 (m, 1H, 17-H), 2.07 (ddd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 6.0 Hz, $^4J_{HH}$ 1.2 Hz, 1H, 18-H_x), 2.12 (ddd, $^2J_{HH}$ 13.0 Hz, $^3J_{HH}$ 6.2 Hz, $^4J_{HH}$ 1.4 Hz, 1H, 16-H_x), 2.49 (s, 3H, *N*-CH_3), 3.23 (dd, $^2J_{HH}$ 10.2 Hz, $^3J_{HH}$ 5.0 Hz, 1H) and 3.24 (dd, $^2J_{HH}$ 10.2 Hz, $^3J_{HH}$ 5.0 Hz, 1H) (CH_2O), 4.18 (br s, 1H, OH), 4.40 (s, 1H, 9-H), 7.08 (dt, $^4J_{HH}$ 1.2 Hz, $^3J_{HH}$ 7.4 Hz, 1H, 7-H), 7.14 (dt, $^3J_{HH}$ 1.2 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 6-H), 7.15–7.22 (complex signal, 2H, 8-H and 12-H), 7.26 (dt, $^4J_{HH}$ 1.2 Hz, $^3J_{HH}$ 7.2 Hz, 1H, 13-H), 7.31–7.34 (dm, $^3J_{HH}$ 7.2 Hz, 1H, 11-H), 7.41–7.43 (dm, $^3J_{HH}$ 7.6 Hz, 1H, 5-H), 7.66–7.68 (dm, $^3J_{HH}$ 7.6 Hz, 1H, 14-H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.62 [CH_3, $Si(CH_3)_2$], 18.2 [C, $SiC(CH_3)_3$], 24.6 (CH_3, *N*-CH_3), 25.8 [CH_3, $SiC(CH_3)_3$], 32.9 (CH_2, C18), 35.1 (CH_2, C16), 42.4 (CH, C17), 48.2 (CH, C9), 63.7 (C, C9a), 63.96 (CH_2, CH_2O), 64.02 (C, C3a), 79.6 (C, C4), 120.9 (CH, C5), 122.9 (CH, C14), 124.4 (CH, C8), 125.9 (CH, C11), 126.7 (2CH, C6 and C12), 126.87 (2CH, C7 and C13), 137.8 (C, C10), 138.2 (C, C8a), 140.5 (C, C15), 141.9 (C, C4a), 180.4 (C, C1), 181.8 (C, C3).

Significant NMR data of 22 from the spectra of the mixture 22/24 (ratio 22/24~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ –0.11 [s, 6H, $Si(CH_3)_2$], 0.79 [s, 9H, $C(CH_3)_3$], 1.02–1.11 (m, 1H, 17-H), 1.73 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 18-H_n), 1.78 (dd, $^2J_{HH}$ 14.0 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 16-H_x), 1.94 (dd, $^2J_{HH}$ 14.0 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 16-H_n), 2.07 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 8.0 Hz, 1H, 18-H_x), 2.44 (s, 3H, *N*-CH_3), 3.11 (dd, $^2J_{HH}$ 10.4 Hz, $^3J_{HH}$ 6.4 Hz, 1H) and 3.24 (dd, $^2J_{HH}$ 10.4 Hz, $^3J_{HH}$ 6.4 Hz, 1H) (CH_2O), 4.22 (br s, 1H, OH), 4.45 (s, 1H, 9-H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –5.56 [CH_3, $Si(CH_3)_2$], 18.1 [C, $SiC(CH_3)_3$], 24.3 (CH_3, *N*-CH_3), 25.7 [CH_3, $SiC(CH_3)_3$], 31.7 (CH_2, C18), 35.5 (CH_2, C16), 43.9 (CH, C17), 49.4 (CH, C9), 64.3 (C, C9a), 64.6 (CH_2, CH_2O), 64.8 (C, C3a), 79.1 (C, C4), 120.9 (CH, C5), 122.4 (CH, C14), 124.3 (CH, C8), 125.3 (CH, C11), 126.8 (2CH, C8 and C12), 126.92 (2CH, C7 and C13), 137.9 (C, C10), 138.1 (C, C8a), 140.6 (C, C15), 141.4 (C, C4a), 180.0 (C, C1), 181.3 (C, C3).

Pyrolysis of the mixture of 13 and 14. In a sublimation equipment (cold finger) open to the air, a mixture of alcohols **13** and **14** (40 mg, 0.11 mmol) was heated to 270–280 ºC for 36 h,

collecting three fractions (total 9 mg), all of them mixtures of anthracene and **6**, as minor components, being the starting mixture of alcohols **13** and **14**, the main components of these mixtures. The not sublimed material (28 mg) contained solely the mixture of alcohols **13** and **14**.

Pyrolysis of the mixture of 19 and 21. In a sublimation equipment (cold finger) open to the air, a mixture of alcohols **19** and **21** (42 mg, 0.11 mmol) was heated to 260–295 ºC for 36 h, collecting a yellow solid (27 mg), that was subjected to column chromatography (silica gel, 35–70 μm, hexane/EtOAc mixtures) to give in order of elution a yellow solid, mixture of anthrone/anthraquinone (20 mg, ratio anthrone/anthraquinone about 1:4 by ^{1}H NMR) (hexane to hexane/EtOAc 95:5) and a light yellow wax, mixture of **6** and starting alcohols **19** and **21** in a ratio **6**/**19**+**21** close to 2:1 (^{1}H NMR) (11 mg, 26% yield of **6**) (hexane/EtOAc 3:2). The not sublimed black residue contained starting alcohols plus degradation products.

5-{[(*t*-Butyldimethylsilyl)oxy]methyl}-2-methyl-5,6-dihydrocyclopenta[c]pyrrole-1,3(2*H*,4*H*)-dione (5). In a sublimation equipment (cold finger) open to the air, a mixture of silyl ethers **22** and **24** (85 mg, 173 μmol) was heated to 250–270 ºC for 26 h, collecting a yellow solid (64 mg), that was subjected to column chromatography (silica gel, 35–70 μm, 6.4 g, hexane/EtOAc mixtures) to give in order of elution anthraquinone as a yellow solid (27 mg, hexane/EtOAc 99:1), compound **5** as yellow oil (22 mg, hexane/EtOAc 98:2), a mixture of **5** and starting products **22**+**24** (3.8 mg, hexane/EtOAc 98:2, ratio **5**/**22**+**24** 1:1, by ^{1}H NMR), and starting products **22**+**24** (23.2 mg, hexane/EtOAc 96:4,) as a white solid. Some degradation products that did not sublimed were also observed. The recovered starting compounds amounted to 25.6 mg (30%) and the yield of isolated **5** was 42% (62%, taking into account the recovered starting material).

(3a*R,9a*R**,17*S**)-4-Hydroxy-17-(methanesulfonyloxymethyl)-2-methyl-4,9-dihydro-4,9-[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (23) and (3a*R**, 9a*R**, 17*R**)-4-hydroxy-17-(methanesulfonyloxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (25).** To a cold solution (0º C, ice-water bath) of a mixture of diols **19** and **21** (74 mg, 197 μmol) and anhydrous Et_3N (60 μL, 46 mg, 450 μmol) in anhydrous CH_2Cl_2 (4 mL) under an argon atmosphere, MsCl (20 μL, 27 mg, 240 μmol) was added dropwise and the mixture was stirred for 4 h at 0 ºC. The solution was taken in EtOAc (10 mL), washed with water (3×5 mL) and brine (2×5 mL). Saturated aqueous solution of $NaHCO_3$ (1 mL) and water (4 mL) were added to the reaction mixture, the organic phase was separated and the aqueous one was extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were dried (anhydrous Na_2SO_4) and concentrated to dryness in vacuo to give a white solid (91 mg), that was subjected to column chromatography (silica gel, 35–70 μm, 5 g, hexane/EtOAc mixtures) to give on elution with hexane/EtOAc 7:3, a mixture of mesylates **23** and **25** in a ratio **23**/**25** about 2:1 (80 mg) as light brown solid. The analytical sample of the **23**/**25** mixture (67 mg, 75% yield) was obtained as white solid by heating the solid with pentane.

Analytical and spectroscopic data of the mixture of 23 and 25: R_f 0.43 (silica gel, 10 cm, hexane/EtOAc 3:7); mp 166–167 ºC (dec.); IR (ATR, ν_{max}, cm^{-1}): 3384w (O–H st), 1767w and 1682s (C=O st), 1354s and 1172s (S=O st). HRMS (ESI-TOF) calcd. for $[C_{24}H_{23}NO_6S+H]^+$:

454.1319. Found: 454.1316. Anal. calcd. for $C_{24}H_{23}NO_6S$: C, 63.56; H, 5.11; N, 3.09; S, 7.07%. Found: C, 63.54; H, 5.10; N, 2.87; S, 6.69%.

NMR data of 23 from the spectra of the mixture 23/25 (ratio 23/25~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, $^2J_{HH}$ 12.6 Hz, 1H, 16-H_n), 1.23 (t, $^2J_{HH}$ 12.8 Hz, 1H, 18-H_n), 2.09–2.21 (m, 1H, 17-H), 2.24 (overlapped ddd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 6.8 Hz, $^4J_{HH}$ 1.2 Hz, 1H, 18-H_x), 2.29 (ddd, $^2J_{HH}$ 13.2 Hz, $^3J_{HH}$ 6.2 Hz, $^4J_{HH}$ 1.4 Hz, 1H, 16-H_x), 2.50 (s, 3H, *N*-CH_3), 2.85 (s, 3H, CH_3SO_3), 3.81 (d, $^3J_{HH}$ 6.0 Hz, 2H, CH_2O), 4.17 (br s, 1H, OH), 4.43 (s, 1H, 9-H), 7.11 (dt, $^3J_{HH}$ 1.2 Hz, $^4J_{HH}$ 7.4 Hz, 1H, 7-H), 7.18 (dt, $^4J_{HH}$ 1.2 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 6-H), 7.19–7.24 (complex signal, 2H, 8-H and 12-H), 7.30 (dt, $^4J_{HH}$ 1.2 Hz, $^3J_{HH}$ 7.6 Hz, 1H, 13-H), 7.34–7.36 (dm, $^3J_{HH}$ 7.2 Hz, 1H 11-H), 7.41–7.43 (dm, $^3J_{HH}$ 7.6 Hz, 1H, 5-H), 7.69 (br d, $^3J_{HH}$ 7.2 Hz, 1H, 14-H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.7 (CH_3, *N*-*C*H_3), 33.1 (CH_2, C18), 35.1 (CH_2, C16), 37.4 (CH_3, CH_3SO_3), 39.2 (CH, C17), 48.0 (CH, C9), 63.6 (C, C9a), 63.9 (C, C3a), 69.4 (CH_2, CH_2O), 79.6 (C, C4), 120.9 (CH, C5), 123.1 (CH, C14), 124.5 (CH, C8), 126.1 (CH, C11), 126.9 (CH, C12), 127.0 (2CH, C6 and C13), 127.1 (CH, C7), 137.6 (C, C10), 137.7 (C, C8a), 140.3 (C, C15), 141.4 (C, C4a), 179.5 (C, C1), 180.9 (C, C3).

Significant NMR data of 25 from the spectra of the mixture 23/25 (ratio 23/25~2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.22 (m, 1 H, 17-H), 1.68 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 8.4 Hz, 1H, 18-H_n), 1.89 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 8.4 Hz, 1H, 16-H_n), 1.96 (dd, $^2J_{HH}$ 14.4 Hz, $^3J_{HH}$ 8.4 Hz, 1H, 16-H_x), 2.20–2.32 (overlapped signal, 1H, 18-H_x), 2.46 (s, 3H, *N*-CH_3), 2.88 (s, 3H, CH_3SO_3), 3.77 (d, $^3J_{HH}$ 5.6 Hz, 2H, CH_2O), 4.22 (br s, 1H, OH), 4.47 (s, 1H, 9-H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.5 (CH_3, *N*-*C*H_3), 32.0 (CH_2, C18), 35.7 (CH_2, C16), 37.1 (CH_3, CH_3SO_3), 40.6 (CH, C17), 49.3 (CH, C9), 64.0 (C, C9a), 64.6 (C, C3a), 71.3 (CH_2, CH_2O), 79.0 (C, C4), 120.9 (CH, C5), 122.5 (CH, C14), 124.4 (CH, C8), 125.3 (CH, C11), 127.0 (CH, C12), 127.07 (CH, C6), 127.13 (CH, C13), 127.2 (CH, C7), 137.5 (C, C10), 137.7 (C, C8a), 140.3 (C, C15), 141.0 (C, C4a), 179.1 (C, C1), 180.4 (C, C3).

Acknowledgements

Financial support from *Dirección General de Investigación* of *Ministerio de Economía y Competitividad* [project CTQ2011-22433 and fellowship to T. Gómez (FPI program)] is gratefully acknowledged. We also thank the *Centres Científics i Tecnològics* of the University of Barcelona (CCiTUB) for NMR and MS facilities, and Ms. P. Domènech from the *Institut de Química Avançada de Catalunya* (IQAC, CSIC, Barcelona, Spain) for the elemental analyses.

References

1. Camps, P.; Gómez, T. ; Monasterolo, C. *J. Org. Chem.* **2012**, *77*, 11270. http://dx.doi.org/10.1021/jo302398c

2. Johns, V. K; Shi, Z.; Dang, W.; McInnis, M. D.; Weng, Y.; Liao, Y. *J. Phys. Chem. A.* **2011**, *115*, 8093. http://dx.doi.org/10.1021/jp202063m
3. Alibert, S.; Santelli-Rouvier, C.; Castaing, M.; Berthelot, M.; Spengler, G.; Molnar, J.; Barbe, J. *Eur. J. Med. Chem.* **2003**, *38*, 253. http://dx.doi.org/10.1016/S0223-5234(03)00018-7
4. Camps, P.; Fernández, J. A.; Rull, J.; Vázquez, S. Eur. *J. Org. Chem.* **2009**, 3081. http://dx.doi.org/10.1002/ejoc.200900273
5. Rickborn, B. *Org. React.* **1998**, *52*, 1–393.
6. Knapp, S.; Ornaf, R. M.; Rodriques, K. E. *J. Am. Chem. Soc*. **1983**, *105*, 5494. http://dx.doi.org/10.1021/ja00354a060
7. Bunnage, M. E.; Nicolaou, K. C. *Angew. Chem. Int. Ed*. **1996**, *35*, 1110. http://dx.doi.org/10.1002/anie.199611101
8. Burgess, K. L.; Corbett, M. S.; Eugenio, P.; Lajkiewicz, N. J.; Liu, X.; Sanyal, A.; Yan, W.; Yuan, Q.; Snyder, J. K. *Bioorg. Med. Chem*. **2005**, *13*, 5299. http://dx.doi.org/10.1016/j.bmc.2005.06.025
9. Bunnage, M. E; Nicolaou, K. C. *Chem. Eur. J*. **1997**, *3*, 187. http://dx.doi.org/10.1002/chen.19970030204
10. Zakarian, A.; Batch, A.; Holton, R. *J. Am. Chem. Soc*. **2003**, *125*, 7822. http://dx.doi.org/10.1021/ja029225v
11. Keck, G.; Truong, A. *Org. lett*. **2005**, *7*, 2153. http://dx.doi.org/10.1021/ol050512o

