

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

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

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Abstract

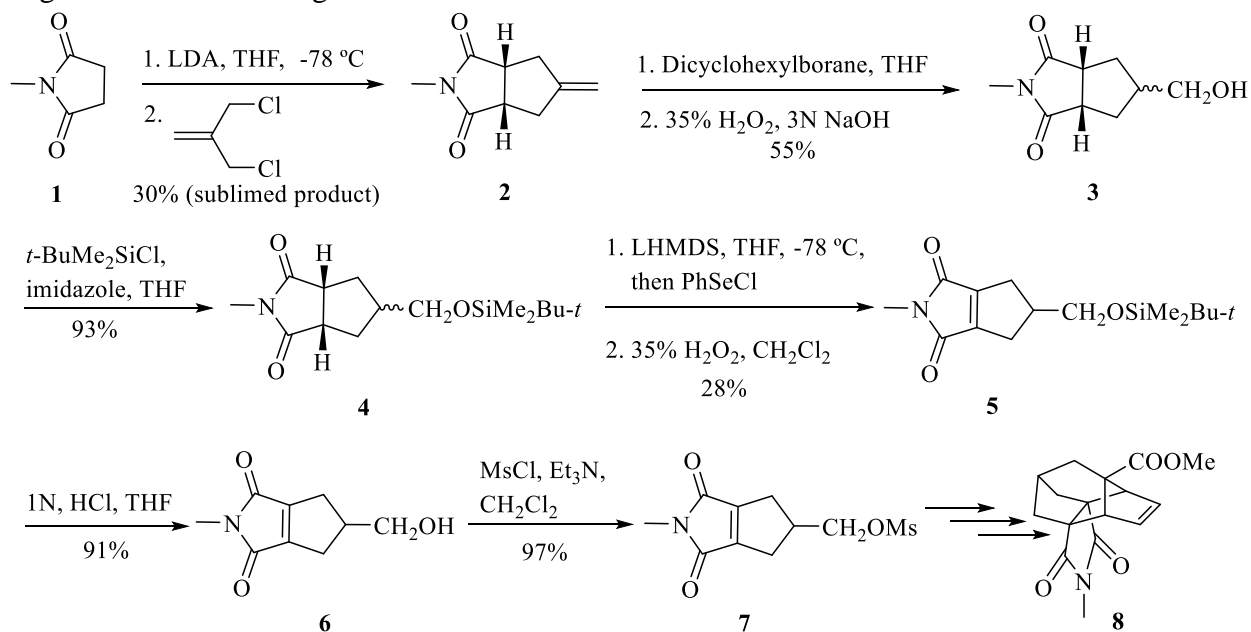
An improved preparation of 5-(*t*-butyldimethylsilyloxymethyl)-2-methyl-5,6-dihydrocyclopenta[*c*]pyrrole-1,3(2*H*,4*H*)-dione, a key intermediate for the preparation of the new polycyclic scaffold, methyl 2-methyl-1,3-dioxo-1,2,3,4,5,6,7,8-octahydro-3a,7,8-(epi)prop[2]ene[1,1,3]triylo-5,8a-methanocyclohepta[*c*]pyrrole-7-carboxylate,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

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

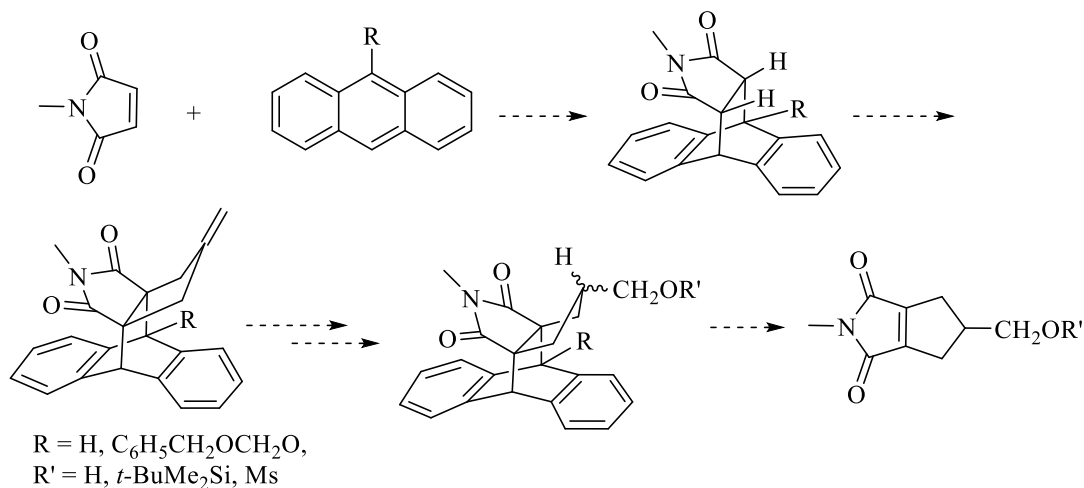
Introduction

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**.

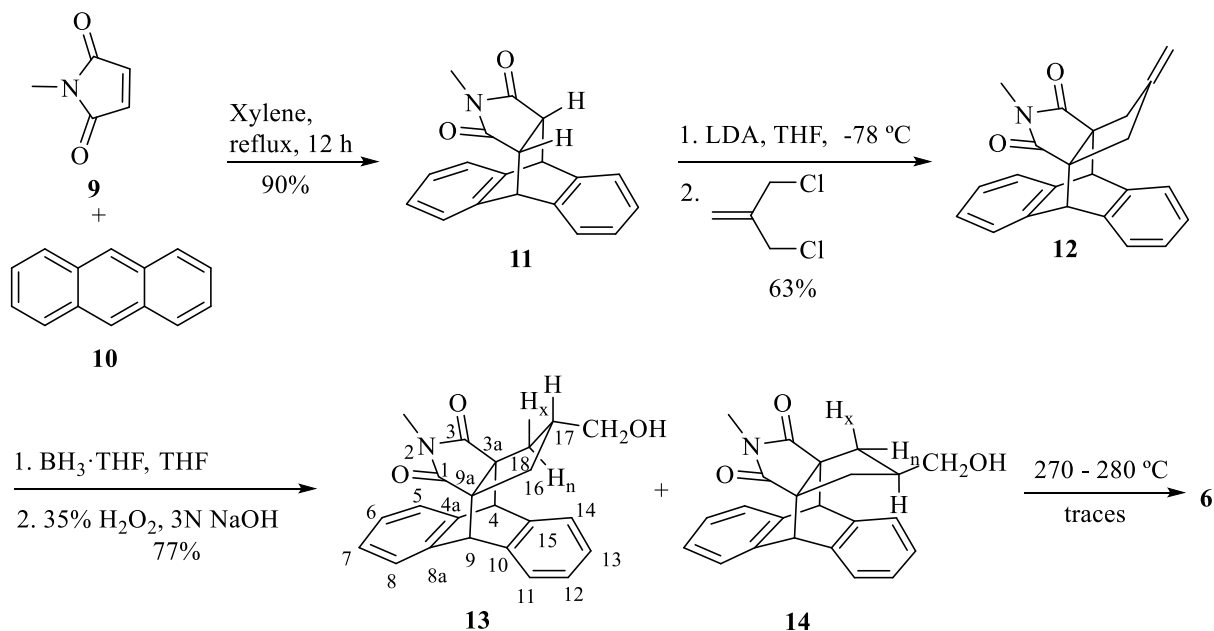


Scheme 2. Proposed alternative synthesis of alcohol **6** and derivatives.

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 BH₃·THF complex, after oxidation with H₂O₂/NaOH, a stereoisomeric mixture of alcohols **13** and **14** in a ratio **13/14** about 2:1 (¹H 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 ¹H/¹H homocorrelation (COSY and NOESY) and ¹H/¹³C heterocorrelation spectra (gHSQC sequence for one bond correlations and gHMBC sequence for long range ones). In this way, the ¹H and ¹³C 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 ¹H 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 °) 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 °C 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 °C in the presence of dimethyl acetylenedicarboxylate or maleic anhydride, the starting mixture of alcohols was recovered unchanged.

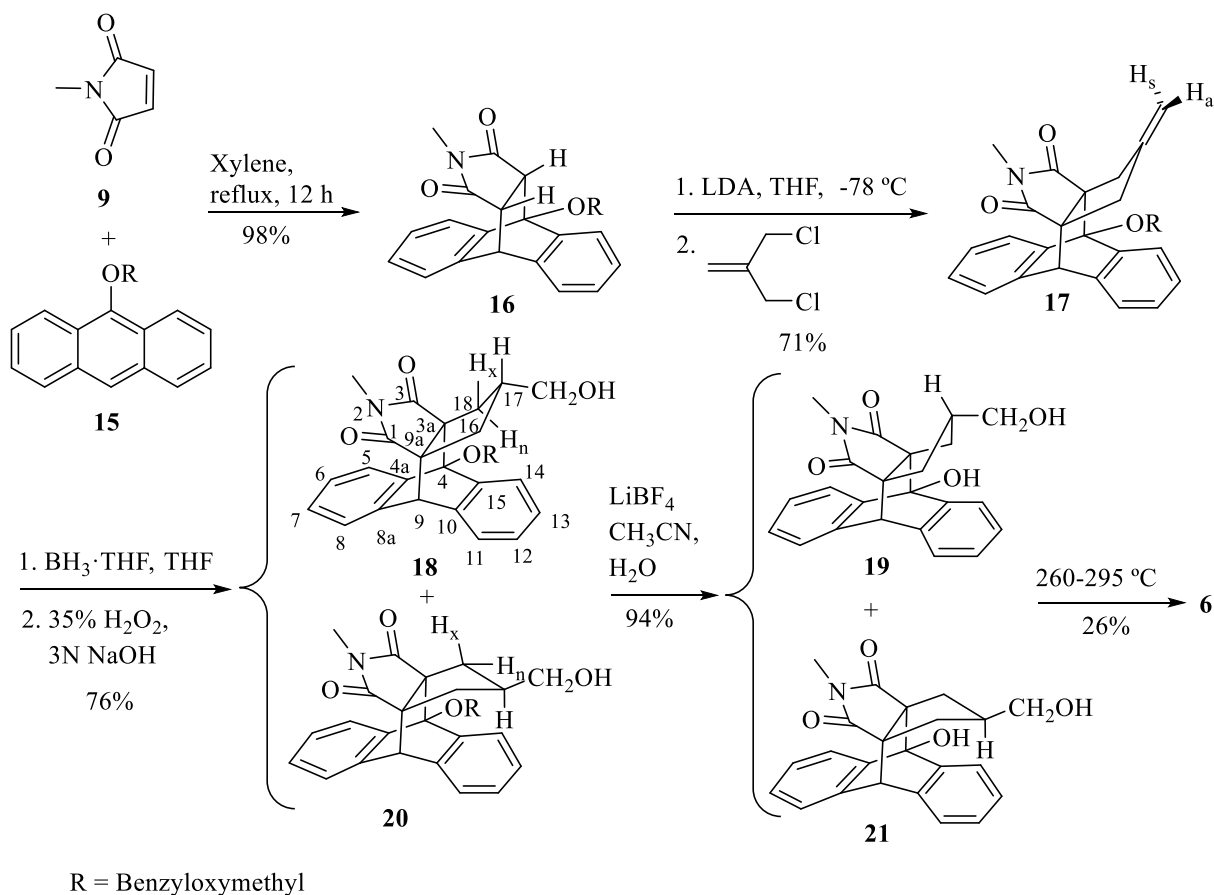
Retro-Diels-Alder reactions of anthracene adducts are usually carried out under flash vacuum pyrolysis (FVP) conditions, although there are several examples of reactions performed at 250–300 °C.⁵ Thus, the above result was not fully unexpected. Knapp et al.⁶ had shown that the Diels-Alder adducts derived 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 °C. 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 $\text{BH}_3\cdot\text{THF}$ complex followed by $\text{H}_2\text{O}_2/\text{NaOH}$ oxidation gave a mixture of alcohols **18** and **20** in a ratio **18/20** about 2:1 (¹H 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 ¹H 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 °) 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 ¹H/¹³C heterocorrelation (gHMBC spectrum) between 9-H and C11 combined with the one bond ¹H/¹³C 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.

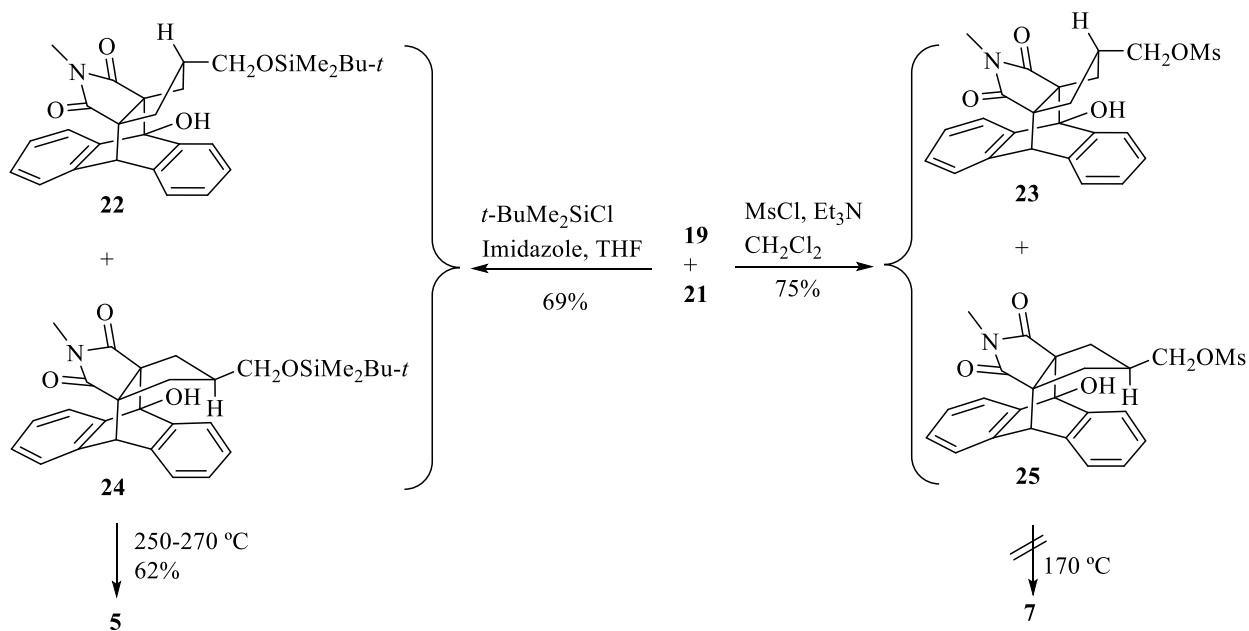


Scheme 4. Preparation of the mixture of diols **19** and **21** from maleimide **9** and anthracene derivative **15** and retro-Diels-Alder reaction of these diols to **6**.

Hydrolysis of the benzyloxymethoxy group of the **18/20** mixture to the **19/21** mixture was carried out in high yield by reaction with LiBF₄ in a mixture CH₃CN/H₂O at 90 °C 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 °C (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 (¹H 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 anthraquinone 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** (¹H 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 °C (over its melting point) in a 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 °C 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-benzyloxymetoxanthracene, (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. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Mercury 400 (400 MHz, 100.6 MHz for ¹³C) spectrometer. Chemical shifts (δ) are reported in ppm related to internal TMS or CDCl₃. 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, ¹H/¹³C single quantum correlation (gHSQC sequence) and ¹H/¹³C 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 F₂₅₄ (Merck, ref. 1.05554) and spots were visualized with UV light, a 1% aqueous solution of KMnO₄. Anthrone was purchased from Alfa Aesar, *N*-methylmaleimide and *t*-butyldimethylsilyl chloride from TCI, anthracene from Merck, benzyloxymethyl chloride and LiBF₄ from Sigma Aldrich, 3-chloro-2-(chloromethyl)-1-propene from Secant Chemical Inc., all of them were used without further purification.

(3aR,9aS)-2-Methyl-17-methylene-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1H-benz-[f]isoindole-1,3(2H)-dione (12). To a cold (–78 °C, acetone/solid CO₂) 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 °C for 1 h, it was cooled again to –78 °C, 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 °C for 15 min and allowed to warm to 0 °C for 1 h. The solution was again cooled to –78 °C 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 Et₂O (3×50 mL). The combined organic extracts were dried (anhydrous Na₂SO₄) 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 °C (from EtOAc/hexane); IR (ATR, ν_{\max} , cm⁻¹): 1770w and 1693s (C=O st); ¹H NMR (400 MHz, CDCl₃) δ 1.65 (br s, H₂O), 2.11 [dt, ²*J*_{HH} 16.4 Hz, ⁴*J*_{HH} 2.4 Hz, 2H, 16(18)-H_n], 2.47 (s, 3H, *N*-CH₃), 2.64 [br d, ²*J*_{HH} 16.4 Hz, 2H, 16(18)-H_x], 4.51 [s, 2H, 4(9)-H], 4.61–4.62 (br s, 2H, C17=CH₂), 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]; ¹³C NMR (100.6 MHz, CDCl₃) δ 24.5 (CH₃, *N*-CH₃), 39.3 [CH₂, C16(18)], 49.5 [CH, C4(9)], 62.0 [C, C3a(9a)], 108.8 (CH₂, C17=CH₂), 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 [C₂₃H₁₉NO₂+H]⁺: 342.1489. Found: 342.1485; Anal. calcd. for C₂₃H₁₉NO₂·0.25H₂O: 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 °C, 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 BH₃·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 °C for 4 h. After addition of EtOH (1.1 mL), the mixture was allowed to warm to room temperature, and aqueous solutions of 35% H₂O₂ (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 Na₂SO₄) 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 (¹H 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 °C; 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 [C₂₃H₂₁NO₃+H]⁺: 360.1594. Found: 360.1591; Anal. calcd. for C₂₃H₂₁NO₃·0.5H₂O: 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): ¹H NMR (400 MHz, CDCl₃) δ 1.01 [t, ²*J*_{HH} = ³*J*_{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 H₂O), 2.21 [dd, ²*J*_{HH} 13.4 Hz, ³*J*_{HH} 6.2 Hz, 2H, 16(18)-H_x], 2.48 (s, 3H,

N-CH₃), 3.22 (d, ³*J*_{HH} 6.4 Hz, 2H, *CH*₂OH), 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]; ¹³C NMR (100.6 MHz, CDCl₃) δ 24.6 (*CH*₂, *N-CH*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): ¹H NMR (400 MHz, CDCl₃) δ 1.20–1.30 (m, 1H, 17-H), 1.80 [dd, ²*J*_{HH} 14.6 Hz, ³*J*_{HH} 7.8 Hz, 2H, 16(18)-H_n], 1.90 [dd, ²*J*_{HH} 14.4 Hz, ³*J*_{HH} 6.4 Hz, 2H, 16(18)-H_x], 2.43 (s, 3H, *N-CH*₃), 3.20 (d, ³*J*_{HH} 6.4 Hz, 2H, *CH*₂OH), 4.50 [s, 2H, 4(9)-H]; ¹³C NMR (100.6 MHz, CDCl₃) δ 24.4 (*CH*₂, *N-CH*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)].

(3aR*,9aR*)-4-[(Benzyloxy)methoxy]-2-methyl-3a,4,9,9a-tetrahydro-4,9[1',2']benzeno-1H-benz[*f*]isoindole-1,3(2H)-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 °C 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 °C (xylene); IR (ATR, *v*_{max}, cm⁻¹): 1693s (C=O st). ¹H NMR (400 MHz, CDCl₃) δ 2.52 (s, 3H, *N-CH*₃), 3.32 (dd, ³*J*_{HH} 8.6 Hz, ³*J*_{HH} 3.0 Hz, 1H, 9a-H), 3.47 (d, ³*J*_{HH} 8.8 Hz, 1H, 3a-H), 4.71 (d, ³*J*_{HH} 3.2 Hz, 1H, 9-H), 5.06 (d, ²*J*_{HH} 11.8 Hz, 1H) and 5.21 (d, ²*J*_{HH} 11.8 Hz, 1H) (OCH₂Ph), 5.64 (d, ²*J*_{HH} 5.6 Hz, 1H) and 5.72 (d, ²*J*_{HH} 6.0 Hz, 1H) (OCH₂O), 7.14 (dt, ⁴*J*_{HH} 1.2 Hz, ³*J*_{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, ³*J*_{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, ³*J*_{HH} 7.2 Hz, 2H, Ph-2(6)-H], 7.65–7.68 (dm, ³*J*_{HH} 7.6 Hz, 1H, 5-H), 7.72–7.75 (dm, ³*J*_{HH} 6.8 Hz, 1H, 14-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 24.3 (*CH*₃, *N-CH*₃), 44.6 (*CH*, C9), 47.4 (*CH*, C3a), 47.9 (*CH*, C9a), 71.4 (*CH*₂, *CH*₂C₆H₅), 81.8 (C, C4), 92.0 (*CH*₂, OCH₂O), 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 [C₂₇H₂₃NO₄+Na]⁺: 448.1519. Found: 448.1513; Anal. calcd. for C₂₇H₂₃NO₄: C, 76.22; H, 5.45; N, 3.29%. Found: C, 76.08; H, 5.55; N, 3.24%.

(3aR*,9aR*)-4-[(Benzyloxy)methoxy]-2-methyl-17-methylene-4,9-dihydro-4,9[1',2']benzene-3a,9a-propano-1H-benz[*f*]isoindole-1,3(2H)-dione (17). To a cold (–78 °C, acetone/solid CO₂ 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 °C for 1 h, it was cooled again to –78 °C, and a solution of **16** (1.65 g, 3.88 mmol) in

anhydrous THF (20 mL) was added dropwise. Then, the solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min and allowed to warm to $0\text{ }^{\circ}\text{C}$ for 1 h. The solution was again cooled to $-78\text{ }^{\circ}\text{C}$ 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 Et₂O (3×50 mL). The combined organic extracts were dried (anhydrous Na₂SO₄) 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 °C (EtOAc/hexane); IR (ATR, ν_{max} , cm⁻¹): 1772w and 1697s (C=O st). ¹H NMR (400 MHz, CDCl₃) δ 2.01–2.04 (dm, ²*J*_{HH} 15.4 Hz, 1H, 16-H_n), 2.26–2.31 (dm, ²*J*_{HH} 15.6 Hz, 1H, 18-H_n), 2.46 (s, 3H, *N*-CH₃), 2.60 (br d, ²*J*_{HH} 15.4 Hz, 1H, 16-H_x), 2.69 (d ancho, ²*J*_{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, ²*J*_{HH} 11.8 Hz, 1H) and 5.17 (d, ²*J*_{HH} 11.8 Hz, 1H) (OCH₂Ph), 5.50 (s, 2H, OCH₂O), 7.13 (overlapped dt, ⁴*J*_{HH} 1.2 Hz, ³*J*_{HH} 7.6 Hz, 1H, 7-H), 7.17 (overlapped dt, ⁴*J*_{HH} 1.6 Hz, ³*J*_{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, ³*J*_{HH} 7.2 Hz, 2H, Ph-3(5)-H], 7.54–7.57 [dm, ³*J*_{HH} 7.2 Hz, 2H, Ph-2(6)-H], 7.76–7.78 (dm, ³*J*_{HH} 7.2 Hz, 1H, 5-H), 7.79–7.82 (dm, ³*J*_{HH} 6.8 Hz, 1H, 14-H). ¹³C NMR (100.6 MHz, CDCl₃) δ 24.6 (CH₃, *N*-CH₃), 38.3 (CH₂, C18), 39.0 (CH₂, C16), 48.7 (CH, C9), 64.0 (C, C3a), 64.8 (C, C9a), 70.5 (CH₂, CH₂C₆H₅), 87.1 (C, C4), 92.1 (CH₂, OCH₂O), 108.9 (CH₂, 17=CH₂), 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 [C₃₁H₂₇NO₄+NH₄]⁺: 495.2278. Found: 495.2273; Anal. Calcd. for C₃₁H₂₇NO₄: C, 77.97; H, 5.70; N, 2.93%. Found: C, 77.56; H, 5.84; N, 2.63%.

(3aR*,9aR*,17S*)-4-(Benzyloxymethoxy)-17-(hydroxymethyl)-2-methyl-4,9-dihydro-4,9-[1',2']benzeno-3a,9a-propano-1H-benz[*f*]isoindole-1,3(2*H*)-dione (18) and (3aR*, 9aR*, 17R*)-4-(benzyloxymethoxy)-17-(hydroxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzeno-3a,9a-propano-1H-benz[*f*]isoindole-1,3(2*H*)-dione (20). To a cold ($0\text{ }^{\circ}\text{C}$, 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 BH₃·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 $0\text{ }^{\circ}\text{C}$ for 4 h. After addition of EtOH (2.3 mL), the mixture was allowed to warm to room temperature, and aqueous solutions of 35% H₂O₂ (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 Na₂SO₄) 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 (¹H 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 °C (EtOAc/hexane); IR (ATR, ν_{\max} , cm⁻¹): 3480w (O–H st), 1770w and 1694s (C=O st). HRMS (ESI-TOF): calcd. for [C₃₁H₂₉NO₅+H]⁺: 496.2118. Found: 496.2111; Anal. calcd. for C₃₁H₂₉NO₅: 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): ¹H NMR (400 MHz, CDCl₃) δ 0.93 (t, ²*J*_{HH} 12.6 Hz, 1H, 16-H_n), 1.0–1.6 (br s, OH), 1.13 (t, ²*J*_{HH} 12.6 Hz, 1H, 18-H_n), 1.85–1.97 (m, 1H, 17-H), 2.17 (ddd, ²*J*_{HH} 13.0 Hz, ³*J*_{HH} 6.0 Hz, ⁴*J*_{HH} 1.4 Hz, 1H, 16-H_x), 2.29 (ddd, ²*J*_{HH} 13.2 Hz, ³*J*_{HH} 6.0 Hz, ⁴*J*_{HH} 1.2 Hz, 1H, 18-H_x), 2.48 (s, 3H, *N*-CH₃), 3.21 (overlapped dd, ³*J*_{HH} 6.0 Hz, 1H, CH_aOH), 3.23 (dd, ²*J*_{HH} 10.6 Hz, ³*J*_{HH} 6.2 Hz, 1H, CH_bOH), 4.41 (s, 1H, 9-H), 5.04 (d, ²*J*_{HH} 12.0 Hz, 1H, CH_aC₆H₅), 5.15 (d, ²*J*_{HH} 12.0 Hz, 1H, CH_bC₆H₅), 5.49 (s, 2H, OCH₂O), 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, ³*J*_{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, ³*J*_{HH} 8.4 Hz, 2H, Ar-2(6)-H], 7.72–7.74 (dm, ³*J*_{HH} 7.2 Hz, 1H, 5-H), 7.79–7.82 (dm, ³*J*_{HH} 7.2 Hz, 1H, 14-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 24.6 (CH₃, *N*-CH₃), 34.5 (CH₂, C18), 35.0 (CH₂, C16), 42.5 (CH, C17), 48.6 (CH, C9), 64.9 (C, C9a), 65.5 (CH₂, CH₂OH), 66.5 (C, C3a), 70.5 (CH₂, CH₂C₆H₅), 87.0 (C, C4), 92.0 (CH₂, OCH₂O), 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): ¹H NMR (400 MHz, CDCl₃) δ 1.10–1.20 (m, 1 H, 17-H), 1.71 (dd, ²*J*_{HH} 14.4 Hz, ³*J*_{HH} 8.0 Hz, 1H, 16-H_n), 1.84 (dd, ²*J*_{HH} 14.4 Hz, ³*J*_{HH} 6.8 Hz, 1H, 18-H_x), 1.84–1.90 (overlapped dd, ³*J*_{HH} 6.4 Hz, 1H, 16-H_x), 2.10 (dd, ²*J*_{HH} 14.4 Hz, ³*J*_{HH} 8.4 Hz, 1H, 18-H_n), 2.42 (s, 3H, *N*-CH₃), 3.17 (dd, ²*J*_{HH} 10.6 Hz, ³*J*_{HH} 6.2 Hz, 1H) and 3.19 (dd, ²*J*_{HH} 10.6 Hz, ³*J*_{HH} 6.0 Hz, 1H) (CH₂OH), 4.44 (s, 1H, 9-H), 5.06 (d, ²*J*_{HH} 11.6 Hz, 1H, CH_aC₆H₅), 5.15 (d, ²*J*_{HH} 11.6 Hz, 1H, CH_bC₆H₅), 5.47 (d, ²*J*_{HH} 6.0 Hz, 1H, OCH_aO), 5.49 (d, ²*J*_{HH} 6.0 Hz, 1H, OCH_bO). ¹³C NMR (100.6 MHz, CDCl₃) δ 24.5 (CH₃, *N*-CH₃), 33.0 (CH₂, C18), 35.2 (CH₂, C16), 43.4 (CH, C17), 49.9 (CH, C9), 65.0 (C, C9a), 65.6 (CH₂, CH₂OH), 66.5 (C, C3a), 70.4 (CH₂, CH₂C₆H₅), 87.6 (C, C4), 92.2 (CH₂, OCH₂O), 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).** LiBF₄ (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 °C for 3 h. The solution was allowed to cool to room temperature, was diluted with CH₂Cl₂ (35 mL) and was washed with H₂O (10 mL), saturated aqueous solution of NaHCO₃ (10 mL) and brine (14 mL). The organic phase was dried (anhydrous Na₂SO₄) 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 °C (EtOAc/hexane); IR (ATR, *v*_{max}, cm⁻¹): 3600–3150 (max. at 3500w, O–H st), 1767w and 1686s (C=O st); HRMS (ESI-TOF): calcd. for [C₂₃H₂₁NO₄+H]⁺: 376.1543. Found: 376.1538: Anal. calcd. for C₂₃H₂₁NO₄: 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): ¹H NMR (400 MHz, CDCl₃) δ 1.1–1.5 (br s, 1H CH₂OH), 1.06 (t, ²*J*_{HH} = ³*J*_{HH} 12.8 Hz, 1H, 16-H_n), 1.15 (t, ²*J*_{HH} = ³*J*_{HH} 13.0 Hz, 1H, 18-H_n), 1.90–2.02 (m, 1H, 17-H), 2.19 (dd, ²*J*_{HH} 13.2 Hz, ³*J*_{HH} 6.0 Hz, 1H, 18-H_x), 2.24 (dd, ²*J*_{HH} 13.2 Hz, ³*J*_{HH} 6.0 Hz, 1H, 16-H_x), 2.49 (s, 3H, *N*-CH₃), 3.19–3.27 (m, 2H, CH₂O), 4.19 (br s, 1H, OH), 4.42 (s, 1H, 9-H), 7.09 (t, ³*J*_{HH} 7.2 Hz, 1H, 7-H), 7.17 (overlapped t, ³*J*_{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, ³*J*_{HH} 7.2 Hz, 1H, 11-H), 7.42 (d, ³*J*_{HH} 7.6 Hz, 1H, 5-H), 7.68 (d, ³*J*_{HH} 7.6 Hz, 1H, 14-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 24.6 (CH₃, *N*-CH₃), 33.4 (CH₂, C18), 35.5 (CH₂, C16), 42.3 (CH, C17), 48.1 (CH, C9), 63.8 (C, C9a), 64.1 (C, C3a), 64.9 (CH₂, CH₂O), 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): ¹H NMR (400 MHz, CDCl₃) δ 1.06–1.27 (m, 1 H, 17-H), 1.74 (dd, ²*J*_{HH} 14.4 Hz, ³*J*_{HH} 6.8 Hz, 1H, 18-H_n), 1.84 (dd, ²*J*_{HH} 14.0 Hz, ³*J*_{HH} 8.0 Hz, 1H, 16-H_n), 1.92–1.98 (overlapped dd, 1H, 16-H_x), 2.12 (dd, ²*J*_{HH} 14.0 Hz, ³*J*_{HH} 8.0 Hz, 1H, 18-H_x), 2.44 (s, 3H, *N*-CH₃), 3.19–3.27 (m, 2H, CH₂OH), 4.22 (br s, 1H, OH), 4.44 (s, 1H, 9-H); ¹³C NMR (100.6 MHz, CDCl₃) δ 24.4 (CH₃, *N*-CH₃), 32.3 (CH₂, C18), 35.8 (CH₂, C16), 43.4 (CH, C17), 49.3 (CH, C9), 64.4 (C, C9a), 65.0 (C, C3a), 65.4 (CH₂, CH₂O), 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 Na₂SO₄) 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 °C (AcOEt/hexane); IR (ATR, ν_{\max} , cm⁻¹): 3530w (O–H st), 1769w, 1688s and 1682s (C=O st). HRMS (ESI-TOF): calcd. for [C₂₉H₃₅NO₄Si+H]⁺: 490.2408. Found: 490.2411. Anal. calcd. for C₂₉H₃₅NO₄Si: 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): ¹H NMR (400 MHz, CDCl₃) δ -0.12 [s, 6H, Si(CH₃)₂], 0.76 [s, 9H, C(CH₃)₃], 1.17 (t, ²*J*_{HH} = ³*J*_{HH} 12.6 Hz, 1H, 16-H_n), 1.26 (t, ²*J*_{HH} = ³*J*_{HH} 12.8 Hz, 1H, 18-H_n), 1.81–1.92 (m, 1H, 17-H), 2.07 (ddd, ²*J*_{HH} 13.2 Hz, ³*J*_{HH} 6.0 Hz, ⁴*J*_{HH} 1.2 Hz, 1H, 18-H_x), 2.12 (ddd, ²*J*_{HH} 13.0 Hz, ³*J*_{HH} 6.2 Hz, ⁴*J*_{HH} 1.4 Hz, 1H, 16-H_x), 2.49 (s, 3H, *N*-CH₃), 3.23 (dd, ²*J*_{HH} 10.2 Hz, ³*J*_{HH} 5.0 Hz, 1H) and 3.24 (dd, ²*J*_{HH} 10.2 Hz, ³*J*_{HH} 5.0 Hz, 1H) (CH₂O), 4.18 (br s, 1H, OH), 4.40 (s, 1H, 9-H), 7.08 (dt, ⁴*J*_{HH} 1.2 Hz, ³*J*_{HH} 7.4 Hz, 1H, 7-H), 7.14 (dt, ³*J*_{HH} 1.2 Hz, ³*J*_{HH} 7.6 Hz, 1H, 6-H), 7.15–7.22 (complex signal, 2H, 8-H and 12-H), 7.26 (dt, ⁴*J*_{HH} 1.2 Hz, ³*J*_{HH} 7.2 Hz, 1H, 13-H), 7.31–7.34 (dm, ³*J*_{HH} 7.2 Hz, 1H, 11-H), 7.41–7.43 (dm, ³*J*_{HH} 7.6 Hz, 1H, 5-H), 7.66–7.68 (dm, ³*J*_{HH} 7.6 Hz, 1H, 14-H). ¹³C NMR (100.6 MHz, CDCl₃) δ -5.62 [CH₃, Si(CH₃)₂], 18.2 [C, SiC(CH₃)₃], 24.6 (CH₃, *N*-CH₃), 25.8 [CH₃, SiC(CH₃)₃], 32.9 (CH₂, C18), 35.1 (CH₂, C16), 42.4 (CH, C17), 48.2 (CH, C9), 63.7 (C, C9a), 63.96 (CH₂, CH₂O), 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): ¹H NMR (400 MHz, CDCl₃) δ -0.11 [s, 6H, Si(CH₃)₂], 0.79 [s, 9H, C(CH₃)₃], 1.02–1.11 (m, 1H, 17-H), 1.73 (dd, ²*J*_{HH} 14.4 Hz, ³*J*_{HH} 7.6 Hz, 1H, 18-H_n), 1.78 (dd, ²*J*_{HH} 14.0 Hz, ³*J*_{HH} 7.6 Hz, 1H, 16-H_x), 1.94 (dd, ²*J*_{HH} 14.0 Hz, ³*J*_{HH} 7.6 Hz, 1H, 16-H_n), 2.07 (dd, ²*J*_{HH} 14.4 Hz, ³*J*_{HH} 8.0 Hz, 1H, 18-H_x), 2.44 (s, 3H, *N*-CH₃), 3.11 (dd, ²*J*_{HH} 10.4 Hz, ³*J*_{HH} 6.4 Hz, 1H) and 3.24 (dd, ²*J*_{HH} 10.4 Hz, ³*J*_{HH} 6.4 Hz, 1H) (CH₂O), 4.22 (br s, 1H, OH), 4.45 (s, 1H, 9-H). ¹³C NMR (100.6 MHz, CDCl₃) δ -5.56 [CH₃, Si(CH₃)₂], 18.1 [C, SiC(CH₃)₃], 24.3 (CH₃, *N*-CH₃), 25.7 [CH₃, SiC(CH₃)₃], 31.7 (CH₂, C18), 35.5 (CH₂, C16), 43.9 (CH, C17), 49.4 (CH, C9), 64.3 (C, C9a), 64.6 (CH₂, CH₂O), 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 °C 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 °C 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 ¹H 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 (¹H NMR) (11 mg, 26% yield of **6**) (hexane/EtOAc 3:2). The not sublimed black residue contained starting alcohols plus degradation products.

5-[[*t*-Butyldimethylsilyloxy]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 °C 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 ¹H 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).

(3*aR,9*aR**,17*S**)-4-Hydroxy-17-(methanesulfonyloxymethyl)-2-methyl-4,9-dihydro-4,9-[1',2']benzo-3*a*,9*a*-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (23) and (3*aR**, 9*aR**, 17*R**)-4-hydroxy-17-(methanesulfonyloxymethyl)-2-methyl-4,9-dihydro-4,9[1',2']benzo-3*a*,9*a*-propano-1*H*-benz[*f*]isoindole-1,3(2*H*)-dione (25).** To a cold solution (0° C, ice-water bath) of a mixture of diols **19** and **21** (74 mg, 197 μmol) and anhydrous Et₃N (60 μL, 46 mg, 450 μmol) in anhydrous CH₂Cl₂ (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 °C. The solution was taken in EtOAc (10 mL), washed with water (3×5 mL) and brine (2×5 mL). Saturated aqueous solution of NaHCO₃ (1 mL) and water (4 mL) were added to the reaction mixture, the organic phase was separated and the aqueous one was extracted with CH₂Cl₂ (2×5 mL). The combined organic phases were dried (anhydrous Na₂SO₄) 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 °C (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 [C₂₄H₂₃NO₆S+H]⁺:

454.1319. Found: 454.1316. Anal. calcd. for C₂₄H₂₃NO₆S: 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): ¹H NMR (400 MHz, CDCl₃) 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-CH₃), 2.85 (s, 3H, CH₃SO₃), 3.81 (d, ³J_{HH} 6.0 Hz, 2H, CH₂O), 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). ¹³C NMR (100.6 MHz, CDCl₃) δ 24.7 (CH₃, N-CH₃), 33.1 (CH₂, C18), 35.1 (CH₂, C16), 37.4 (CH₃, CH₃SO₃), 39.2 (CH, C17), 48.0 (CH, C9), 63.6 (C, C9a), 63.9 (C, C3a), 69.4 (CH₂, CH₂O), 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): ¹H NMR (400 MHz, CDCl₃) 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-CH₃), 2.88 (s, 3H, CH₃SO₃), 3.77 (d, ³J_{HH} 5.6 Hz, 2H, CH₂O), 4.22 (br s, 1H, OH), 4.47 (s, 1H, 9-H). ¹³C NMR (100.6 MHz, CDCl₃) δ 24.5 (CH₃, N-CH₃), 32.0 (CH₂, C18), 35.7 (CH₂, C16), 37.1 (CH₃, CH₃SO₃), 40.6 (CH, C17), 49.3 (CH, C9), 64.0 (C, C9a), 64.6 (C, C3a), 71.3 (CH₂, CH₂O), 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).

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