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Synthesis and In Vitro Trypanocide Activity of Several Polycyclic Drimane-Quinone Derivatives

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Abstract—The Diels–Alder reaction between two polygodial-derived dienes and simple quinones to yield substituted naphtho- and anthraquinones, is described. The in vitro trypanocide activity for the series was determined. Two of the new compounds showed an activity ten and two times higher, respectively, than nifurtimox and benznidazole, the medicines of choice for the treatment of the acute Chagas' disease.

Introduction

Together with malaria, leishmaniasis and African trypanosomiasis (sleeping sickness), Chagas' disease is a major cause of death and hardship, especially in the impoverished regions of the developing world. Chagas' disease is widely distributed in all Americas, and it is endemic in 21 countries, from Mexico at the north, to Argentina and Chile at the south. According to the World Health Organization there are 16–18 million people already infected, and some 100 million (25% of Latin America population) at risk of becoming infected, with more than 50,000 people dying every year.[1]

Chagas' disease, or American Trypanosomiasis, is a serious parasitic ailment in Latin America.[2] The World Bank estimated an annual loss of 2.74 million disability-adjusted life years, representing an economic loss to the endemic countries equivalent to U$S 6.5 billion per annum.[3]

Chagas' disease is caused by *Trypanosoma cruzi*, a flagellated protozoan transmitted to humans either by transfusion of infected blood, from an infected mother to her child, or by its most important vector, a blood-sucking bug (a.k.a. '*vinchuca*', '*chipo*', '*barbeiro*', kissing bug, cone nose, or assassin bug), which carries the parasite in its contaminated feces. Contagion usually occurs by contact of the bug's feces with the eyes, mouth, or open skin lesions. Most efforts of controlling the problem are being focused in the bug control. However, even if it could be immediately eradicated, as the disease evolution persists for decades, and only ends with the host's death, there would be many patients with the chronic variant, a real reservoir for the protozoa that would be an open door to reinfectation of general public.

In about one-third of all acute cases, a chronic form develops around 10–20 years later, causing irreversible damage to heart, esophagus and colon, with severe disorders of nerve conduction of these organs. Patients with severe chronic disease become progressively more ill, and ultimately die, usually from their heart condition.

To present, there is no effective treatment for chronic cases, neither a vaccine nor preventive treatment. In the acute, recent or congenital disease, there are two drugs available for treatment: *nifurtimox* (manufactured by Bayer under the trade name Lampit™), a nitrofuran derivative, and *benznidazole* (made by Roche under the trade names Radanil™, Rochagan™ or Roganil™), a

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nitroimidazole derivative.[4] Both compounds have low efficacy and severe side effects, and unfortunately, it was recently decided to discontinue the production of *nifurtimox*. A serious problem associated to both drugs is their rather small therapeutic window (difference between LD_{50} and ED_{50}), and the serious side effects observed, particularly in adult patients.[5] Both drugs are believed to kill or inhibit the growth of the parasites by increasing their oxidative stress.[6,7]

There are several natural compounds of a mixed biogenesis based on farnesyl hydroquinone,[8] like the feeding-deterrent compound cyclozonarone (**1**), recently synthesized in both absolute configurations,[9,10] the cytotoxic, antiviral and antifungal sponge metabolite puupehenone (**2**),[11–13] the antiviral and anti-tuberculosis 15-cyanopuupehenol (**3**), the antimalarial 15-oxopuupehenol (**4**),[14] hyatellaquinone (**5**),[15,16] and the antifungal agent sicannin (**6**).[17] Other natural quinoid active compounds include antiparasitic plumbagin (**7**) and lawsone (**8**)[18] (Fig. 1). The trypanocidal activity of several natural *p*-quinones has been recently reviewed.[19,20]

As these natural compounds containing a quinone or hydroquinone and a drimane sesquiterpene skeleton show such a wide range of important bioactivities, we reasoned that synthetic compounds with the same structural features combined, as in structure **10** could be interesting synthetic targets, easily prepared in a single step by a Diels–Alder reaction of a 1,3-diene like **11**, itself prepared from naturally occurring, commercially available polygodial (**9**), and a 1,4-benzo- or naphthoquinone of type **12**, followed by an aromatization of the resulting adducts (Scheme 1).[21–26] We also foresaw that analogues of *ent*-cyclozonarone [(+)-**1**] of type **13** could also be easily prepared by the very same route that was previously used by us and others in the total synthesis of **1**,[9,10] so giving us access to a series of compounds which might show an interesting biological activity. The synthesis in this case started with the previously described 1,3-diene **14** (Scheme 2),[10] also prepared from polygodial (**9**), which was submitted to a Diels–Alder reaction with several commercially available substituted 1,4-benzo- and naphthoquinones of structure **12**, followed again by an aromatization of the adducts (Scheme 4).

Results and Discussion

When dialdehyde **9**, obtained from the hexanes extract of the bark of *Drymis winteri Forst.*,[26–31] was treated with one equivalent of ethylene glycol in benzene, in the presence of a catalytic amount of *p*-toluenesulfonic acid, monoacetals **15** and **16** were produced in a 62% and 30% yield, respectively (Scheme 3). The conversion of unsaturated aldehyde **15** to diene **17** was rather cumbersome, either plainly failing or giving very low yields of diene under most of the standard Wittig conditions

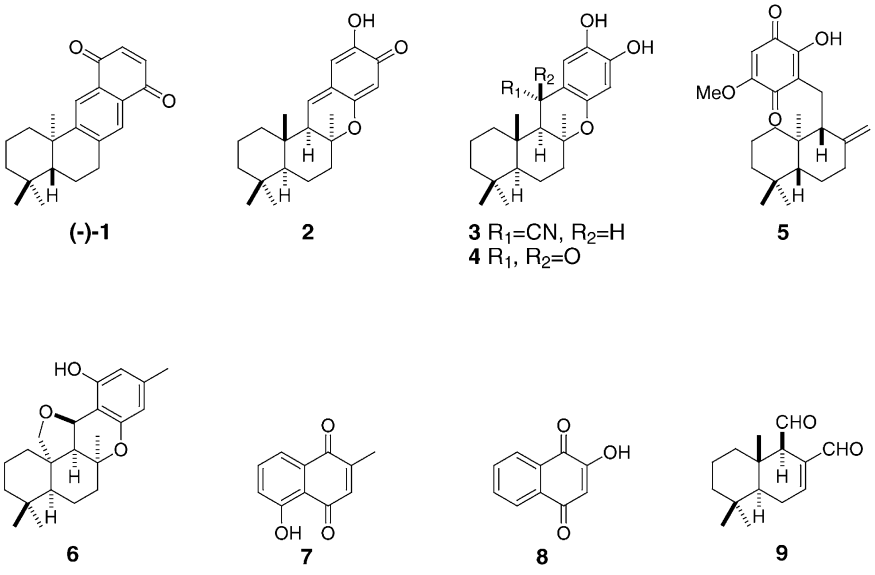
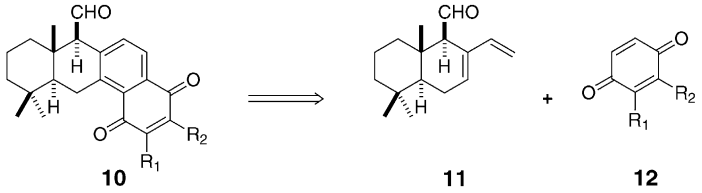


Figure 1.



Scheme 1.

we tried. Fortunately, we found that Tebbe's reagent reacted smoothly with **15**,[32–35] giving us access to the desired diene **17** in a 64% yield.

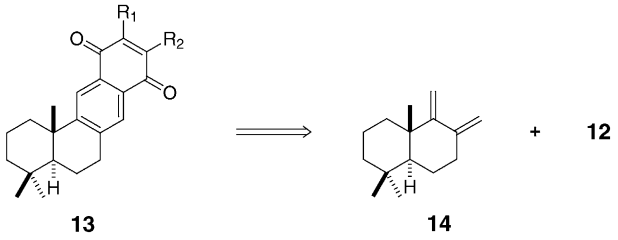
To our delight, when dial **9** was directly treated with one equivalent of the bulky Tebbe's reagent, monoaldehyde **11** was smoothly obtained in a 37% yield, without any observable epimerization at C-1, as the sole product (Scheme 2). If wanted, aldehyde **11** could be further protected as acetal **17**, under the same conditions as mentioned above for the preparation of **15** and **16**.

When diene **11** was treated with 1,4-naphthoquinone (**18**) in refluxing benzene for 2 h (Scheme 3), it gave rise to adduct **19**, as a chromatographically inseparable 4:1 mixture of epimers at C-8, as revealed by the appearance of two low-field aldehyde signals in the ^{1}H NMR spectrum. Treatment of **19** with DBU gave access to aromatic product **20**, again as a mixture of epimers at C-8 that we were unable to separate.

To avoid the formation of epimers at C-8, we decided to carry out the Diels–Alder reaction of diene **17** instead of diene **11**, with a series of commercially available 1,4-quinones as the dienophiles (Fig. 2): 1,4-benzoquinone (**21**), 2,3-dimethyl-1,4-benzoquinone (**22**), 1,4-naphthoquinone (**18**), juglone (**23**) and naphthazarin (**24**). In all cases, the reactions were carried out in refluxing benzene for 2 h, and the crude reaction mixtures were treated with DBU in an open container (under air) to accomplish the aromatization. This gave us access to a series of acetal quinones **25**–**30** (Fig. 3). The results are summarized in Table 1.

The structural assignments for all new compounds were performed by a careful analysis and extensive use of ^{1}H and ^{13}C NMR spectra, with help of a combination of 1D and 2D spectra, also and especially including heteronuclear multiple-bond correlations (HMBC).

The full spectral assignment for the case of regioisomers **29** and **30** is as follows. The major and more polar compound was assigned structure **29**. It showed a proton signal at δ 7.60 ppm, which was unambiguously assigned to H-3 because it is the only aromatic signal with two different *ortho*- coupling constants. Both signals with homonuclear couplings with H-3 therefore correspond to H-2 and H-4. The one at δ 7.74 shows HMBC with a carbonyl signal at δ 183.2 ppm, so it was assigned to H-4, and the carbonyl signal, to C-5. This



Scheme 2.

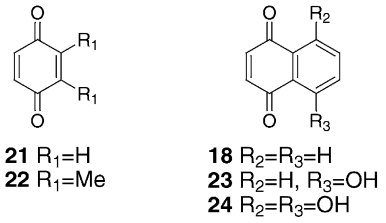
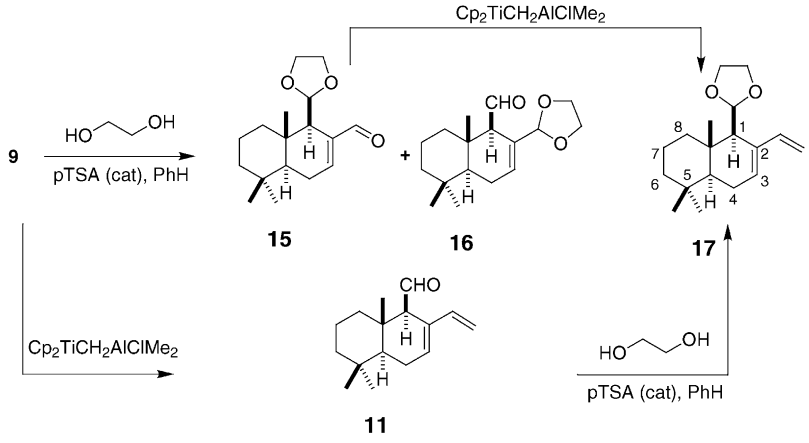
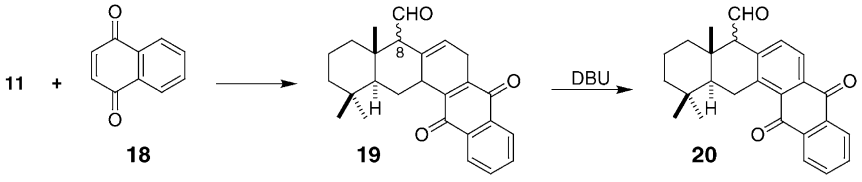


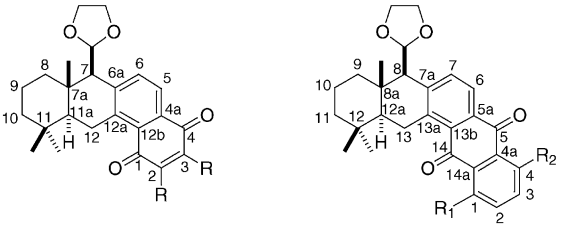
Figure 2.



Scheme 3.



Scheme 4.



25 R=H
26 R=Me

27 R_1=R_2=H
28 R_1=R_2=OH
29 R_1=OH, R_2=H
30 R_1=H, R_2=OH

Figure 3.

Table 1. Diels–Alder reactions of diene **17** with selected quinones (see text for experimental details)

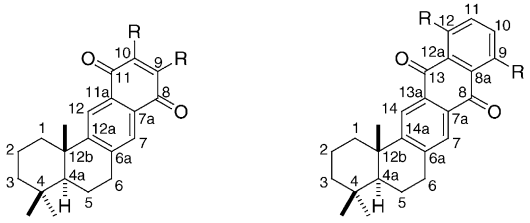
Entry	Starting Quinone[a]	Product/s	Yield%[b]
1	**21**	**25**	58
2	**22**	**26**	62
3[b]	**18**	**27**	73
4	**24**	**28**	54
5	**23**	**29**	
30	**64**		
22			

[a]All reactions were run with diene **17** for 2 h, in refluxing benzene.
[b]Isolated yields, after aromatization.

Table 2. Diels–Alder reactions of diene **14** with selected quinones (see text for experimental details)

Entry	Starting Quinone[a]	Product/s	Yield%[b]
1	**21**	**1**	49
2	**22**	**31**	41
3	**18**	**32**	61
4	**24**	**33**	95

[a]All reactions were run with diene **14**, in refluxing benzene.
[b]Isolated yields, after aromatization.



1 R=H
31 R=Me

32 R=H
33 R=OH

Figure 4.

C-5 signal also showed HMBC with a proton signal at δ 8.07, consequently assigned to H-6. The remaining resonance at δ 7.26 was then assigned to H-2, and the signal at δ 8.14, to H-7.

The proton signal at δ 5.19, unambiguously assigned according to its chemical shift to the acetal proton, $C\underline{H}O_2$, showed HMBC with C-8a, at δ 34.4, C-8, at δ 55.6, and C-7a, at δ 143.0 ppm. The C-8a signal also showed HMBC with a proton frequency at δ 2.10, subsequently assigned to H-9. The multiplet at δ 1.34–1.26 that integrates for two protons was assigned to the remaining H-9 and H-12a signals. This multiplet showed HMBC with a signal at δ 143.1, assigned in consequence to C-13a. The resonances at δ 3.46, assigned to H-13α, and at δ 3.22, assigned to H-13β, both showed HMBC with a carbon at δ 130.5, thus assigned to C-13b. The frequency at δ 132.8 ppm, therefore, could be assigned to C-5a, that also showed HMBC with H-6 and H-7.

The carbon frequency at δ 117.4 ppm, attributed to C-14a, showed HMBC with H-2 and H-4, confirming its assignment. Finally, the signal at δ 133.1 has to be assigned to C-14a. An HSQC spectrum allowed full assigning of the rest of the molecule (see Experimental for full details).

The minor, less polar regioisomer was assigned structure **30** by a similar analysis. Most signals were almost identical in the ^{1}H and ^{13}C spectra of both isomers, except in the aromatic-quinone region. In this case, an HMBC was observed between the signal at δ 12.57, assigned to the OH, with C-4a, at δ 116.0, C-3 at δ 123.4, and C-4 at δ 162.2 ppm. Thus, the signal at δ 7.64 with 2 *ortho* coupling constants belongs to H-2, and the one at δ 7.76, to H-1. The remaining signal at δ 7.23 corresponds to H-3. H-1 shows HMBC with a carbonyl signal at δ 185.1, hence assigned to C-14. Finally, the signal at δ 8.13, assigned H-6 and H-7, shows HMBC with C-5, at 189.5 ppm. This completed the assignment.

On the other hand, treatment of exocyclic 1,3-diene **14** with quinones **21**, **22**, **18** and **24** followed by aromatization with DBU/air produced sesquiterpene-naphthoquinones **1**, **31**, and anthraquinones **32** and **33**, respectively. Results are summarized in Table 2 (Fig. 4).

Table 3 shows the effect of all synthetic quinones, together with the effect of the starting quinones and the established drugs nifurtimox and benznidazole, on the growth of *T. cruzi* epimastigotes, Tulahuen strain. The relative efficacies were expressed as the IC_{kc50} value.

Compounds **1**, **18** and **23** resulted roughly 10 times more active, and compounds **24** and **25** were about twice more active than nifurtimox and benznidazole. The common structural feature in all these compounds is the presence of a 2,3-unsubstituted naphthoquinone moiety.

Compounds **21** and **22** were roughly one half, compound **31** was about 5 times less active, compound **27** resulted about 7 times less active and compound **32** was some 10 times less active than the reference substances. These compounds are 1,4-benzoquinones, 2,3-dimethyl 1,4-naphthoquinones, or substituted anthraquinones.

Table 3. Effect of quinone derivatives **1**, **18** and **21–33** on the culture growth of *T. cruzi* epimastigotes (Tulahuen strain)

Compd	IC_{kc50} (μM)[a]
1	0.7±0.05
18	0.7±0.07
21	25.6±0.61
22	27.0±1.56
23	0.5±0.02
24	5.6±0.48
25	4.9±0.94
26	>100
27	60.6±9.25
28	>100
29	>100
30	>100
31	40.0±2.35
32	84.4±13.10
33	>100
Nifurtimox	9.91±0.2[b]
Benznidazole	11.44±0.1[b]

Note: All values were expressed as the mean±SD of three or more independent experiments.
[a]Inhibition of epimastigotes growth. The IC_{kc50} corresponds to the concentration of drug needed to inhibit 50% control culture growth.
[b]See Ref. 36.

Compounds with an IC_{kc50} greater than 100 μM were considered as having no activity (that was the highest tested concentration), as is the case with **26**, **28**, **29**, **30** and **33**. All these compounds correspond to substituted anthraquinone derivatives.

The protozoacide activity of several 1,4-naphthoquinones against *T. cruzi* was previously described.[18,19,37] It is believed that the mechanism of action of naphthoquinone derivatives involves their absorption by the parasites and subsequent reduction to semiquinones and quinols.[38] These compounds are capable of reducing molecular oxygen into hydrogen peroxide and superoxide anions, thus forming hydroxyl radicals which cause damage to the parasite plasmatic membrane and also inhibit some biosynthetic pathways. Trypanocide activity is believed to involve the generation of oxygenated intracellular species, so it must be related with the compound lipophilicity (related with the size and polarity) and its reduction potential (related with the electron-withdrawing ability).[39] 1,4-naphthoquinones can also be considered as subversive substrates of trypanothione reductase.[40–42]

We observed that in order to have an active compound, a 2,3-unsubstituted naphthoquinone is required, and that an increase in molecular size or substitution leads to a lower bioactivity. The substituted mono- and dihydroxyanthraquinone derivatives **28**, **29**, **30** and **33** probably have too low lipophilic character to be able to enter the parasite cells. In the remaining compounds, a possible explanation of the observed behavior relies on their electron-withdrawing ability, directly related to the experimental half-wave potentials. According to the literature,[43] 2,3-dimethyl-1,4-naphthoquinone and 9,10-anthraquinone have similar potentials (around −0.85 V), on the other hand, 1,4-naphthoquinone has a rather larger potential (of about −0.63 V). Consequently, compounds **1** and **25** are the best oxidants in this series, and also the most active compounds.

Experimental

All reactions were routinely run in open flasks under air with magnetic stirring. All chemicals were used as purchased, or purified according to standard procedures. All melting points were determined in a Stuart Scientific Apparatus SMP3, and are uncorrected. Optical rotations were measured in $CHCl_3$ solutions, in a 0.1 dm cell, in an Optical Activity, Ltd instrument. Infrared spectra were recorded in a Bruker Vector-22 spectrometer. The ^1H and ^{13}C NMR spectra were obtained on a Bruker AC 200P or Avance 400 spectrometer, for $CDCl_3$ solutions with TMS as internal standard. For 2D, COSY, NOE, HSQC and HMBC experiments, Bruker standard software was employed. Symbols *, #, ^ etc., were used to denote signal pairs with interchangeable assignments. Elemental analyses were obtained in a Fisons Instruments EA 1108 microanalyzer. Column chromatography was performed on silica gel 60H, slurry packed, run under low pressure of air, and employing increasing amounts of ethyl acetate in hexane as solvent. Analytical TLC was carried out using Kieselgel Merck F_{254} with thickness 0.20 mm.

Parasites

Trypanosoma Cruzi epimastigotes Tulahuen strain, from our own collection, were grown at 28 °C in Diamond's monophasic medium, as reported earlier,[44] with blood replaced by 4 μM hemin. Fetal calf serum was added to a final concentration of 4%.

Inhibition of culture growth and IC_{kc50} values

Compounds **1**, **18**, and **21–33**, dissolved in dimethylsulfoxide (DMSO, 1% final concentration) were added to a suspension of 3×10^6 epimastigotes/mL. Final concentrations were between 100 and 0,1 μM for each compound. Parasite growth was followed by nephelometry for 10 days.[45] No toxic effect of DMSO alone was observed.

From the epimastigote exponential growth curve, we calculated the culture growth constant (k_c) for each drug concentration treatment and for controls (regression coefficient >0.9, $P<0.05$). This constant corresponds to the slope resulting from plotting the natural logarithm (Ln) of nephelometry lecture versus time.[45]

IC_{kc50} is the drug concentration needed to reduce the k_c in 50% and it was calculated by lineal regression analysis from the k_c values and the concentrations used at the employed concentrations. Values are expressed as the mean + S.D. of three or more independent experiments.

Statistical analysis

Pearson's correlation and linear regression analysis were performed using Prism Graphpad software from Graphpad Software Inc.

(+)-(1*R*,4a*S*,8a*S*)-2-(5,5,8a-Trimethyl-2-vinyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-yl)-[1,3]dioxolane (17). To a solution of polygodial (**9**, 500 mg, 2.14 mmol) in anhydrous benzene (30 mL), contained in a 50 mL round-bottom flask, ethylene glycol (137 mg, 120 μL, 2.20 mmol) was added in the presence of a crystal of *p*-toluenesulfonic acid. A Dean–Stark trap was fitted to the flask, and the solution was refluxed for 12 h, diluted with ethyl acetate, and the organic phase was washed with saturated $NaHCO_3$, dried with magnesium sulfate, and evaporated. The yellowish residue was purified by column chromatography to yield **15** (368 mg, 62%), and **16** (178 mg, 30%).

Method A. Aldehyde **15** (500 mg, 1.88 mmol) was dissolved in anhydrous THF (5 mL) and cooled at 0 °C. Tebbe's reagent (4 mL of a 0.5M solution, 2.0 mmol) was added dropwise. The resulting dark brown mixture was allowed to warm to room temperature for 10 min, diluted with diethyl ether (20 mL), and diluted NaOH solution (0.1M, 10 drops) was added. Some bubbling was observed at this point. $MgSO_4$ was added, and the slurry was filtered through a short pad of silica gel. The filtrate was evaporated in vacuo, and chromatographically purified, to give diene-acetal **17** (330 mg, 64%) as a colorless solid: mp 73.6–74.8 °C (AcOEt); $[\alpha]_D^{16}$ +75.8 (*c* 8.58); IR (KBr) 1613, 1145, 1130 cm^{-1}; ^1H NMR (200 MHz) δ: 6.41 (1H, dd, *J* = 10.8, 17.3 Hz, = C<u>H</u>-C2), 6.00 (1H, m, H-3), 5.20 (1H, dd, *J* = 2.2, 17.3 Hz, = C<u>H</u>$_2$), 5.02 (1H, s, C<u>H</u>O$_2$), 4.77 (1H, dd, *J* = 2.2, 10.8 Hz, = C<u>H</u>$_2$), 4.04–3.72 (4H, m, O-C<u>H</u>$_2$), 2.50 (1H, bs, H-1), 2.08–1.93 (3H, m), 1.61–1.11 (6H, m), 0.95 (3H, s, 7a-<u>Me</u>), 0.91 (3H, s, 5-α-<u>Me</u>), 0.88 (3H, s, 5-β-<u>Me</u>); ^{13}CNMR (50 MHz) δ: 139.5 (= <u>C</u>H), 135.4 (C-2), 125.5 (C-3), 110.2 (= <u>C</u>H$_2$), 103.5 (O-<u>C</u>-O), 65.5 (O-<u>C</u>H$_2$), 63.3 (O-<u>C</u>H$_2$), 55.1 (C-1), 49.5 (C-4a), 42.0 (C-6), 40.1 (C-8), 35.3 (C-8a), 33.4 (5-α-<u>Me</u>), 32.9 (C-5), 23.5 (C-4), 22.1 (5-β-<u>Me</u>), 18.6 (C-7), 14.9 (8a-<u>Me</u>); analysis: calculated for $C_{18}H_{28}O_2$, C = 78.21%, H = 10.21%, found: C = 78.56%, H = 10.09%.

Method B. Polygodial (**9**, 500 mg, 2.14 mmol) was dissolved in anhydrous THF (5 mL), the solution stirred at 0 °C under nitrogen, and Tebbe's reagent (4 mL of a 0.5M solution in toluene, 2.0 mmol) was added dropwise. The dark brown solution was allowed to warm to room temperature for 10 min, 0.1M NaOH solution was added (10 drops) and the slurry was filtered through a short pad of silica gel. The filtrate was rotavapored, and column chromatographed, to give aldehyde **11** (183 mg, 37%) as a colorless oil: $[\alpha]_D^{20}$ −17.3 (*c* 10.98); IR (KBr) 3090, 2720, 1719, 1643, 1607 cm^{-1}; ^1H NMR (200 MHz) δ: 9.45 (1H, d, *J* = 5.1 Hz, CHO), 6.32 (1H, dd, *J* = 11.3, 18.0 Hz, = C<u>H</u>-C2), 6.08–6.11 (1H, m, H-3), 4.89 (1H, d, *J* = 11.3 Hz, = C<u>H</u>$_2$), 4.79 (1H, d, *J* = 18.0 Hz, = C<u>H</u>$_2$) 2.78 (1H, bs, H-1) 2.13–2.22 (2H, m, H-4), 1.77–1.85 (1H, m, H-8), 1.12–1.51 (6H, m), 1.00 (3H, s, 8a-<u>Me</u>), 0.93 (3H, s, 5-α-<u>Me</u>), 0.88 (3H, s, 5-β-<u>Me</u>); ^{13}C NMR (50 MHz) δ: 206.7 (CHO), 138.5 (= <u>C</u>H), 132.8 (C-3), 131.5 (C-2), 112.4 (= <u>C</u>H$_2$), 62.6 (C-1), 48.9 (C-4a), 41.9 (C-6), 40.2 (C-8), 37.3 (C-8a), 33.3 (5-α-<u>Me</u>), 33.1 (C-5), 24.1 (C-4), 22.3 (5-β-<u>Me</u>), 18.6 (C-7), 15.5 (8a-<u>Me</u>).

General procedure for the preparation of quinones 25–30. Diene **17** (50 mg, 0.18 mmol) was dissolved in benzene (15 mL) and a quinone (0.37 mmol), was added to the solution, which was stirred at reflux for 2 h, after which TLC analysis showed the disappearance of the starting material. The solution was allowed to cool to room temperature, and DBU (3 drops) was added with stirring. After an additional 15 min, the reaction mixture was concentrated in rotavapor, and the residue purified by column chromatography, to yield the pure quinone.

(−)-(7*R*,7a*S*,11a*S*)-7-[1,3]Dioxolan-2-yl-7a,11,11-trimethyl-7,7a,8,9,10,11,11a,12-octahydro-benzo[*a*]anthracene-1,4-dione (25). Yield: 58%, yellow solid: mp 175.7–176.5 °C (AcOEt); $[\alpha]_D^{20}$ −73.2 (*c* 2.87); IR (KBr) 1656, 1294 cm^{-1}; ^1H NMR (200 MHz) δ: 8.08 (1H, d, *J* = 8.4 Hz, H-6), 7.88 (1H, d, *J* = 8.4 Hz, H-5), 6.85 (2H, s, H-3 + H-2), 5.18 (1H, s, C<u>H</u>O$_2$), 4.19–4.14 (1H, m, O-C<u>H</u>$_2$), 3.94–3.84 (3H, m, O-C<u>H</u>$_2$), 3.35 (1H, dd, *J* = 4.1, 19.2 Hz, H-12), 3.18 (1H, s, H-7), 3.07 (1H, dd, *J* = 13.2, 19.2 Hz, H-12), 2.09 (1H, bd, *J* = 14.0 Hz, H-8), 1.60–1.26 (6H, m), 1.10 (3H, s, 11-β-<u>Me</u>), 0.98 (3H, s, 11-α-<u>Me</u>), 0.97 (3H, s, 7a-<u>Me</u>); ^{13}C NMR (50 MHz) δ: 187.5 (C-1), 185.8 (C-4), 142.6 (C-6a), 141.8 (C-12a), 140.8 (C-3)*, 136.3 (C-2)*, 134.6 (C-6), 131.4 (C-4a), 129.2 (C-12b), 123.4 (C-5), 103.4 (O-<u>C</u>H-O), 65.5 (O-C<u>H</u>$_2$)#, 63.6 (O-C<u>H</u>$_2$)#, 55.5 (C-7), 49.1 (C-11a), 42.1 (C-10), 40.4 (C-8), 34.5 (C-7a), 33.3 (11-α-<u>Me</u>), 33.2 (C-11), 27.3 (C-12), 22.1 (11-β-<u>Me</u>), 18.6 (C-9), 15.3 (7a-<u>Me</u>); analysis: calculated for $C_{24}H_{28}O_4$, C = 75.76%, H = 7.42%, found: C = 75.23%, H = 7.17%.

(−)-(7*R*,7a*S*,11a*S*)-7-[1,3]Dioxolan-2-yl-2,3,7a,11,11-pentamethyl-7,7a,8,9,10,11,11a,12-octahydro-benzo[*a*]-anthracene-1,4-dione (26). Yield: 62%, yellow solid: mp 151.5–152.2 °C (AcOEt); $[\alpha]_D^{14}$ −115.4 (*c* 2.86); IR (KBr) 1654, 1631, 1582, 1569 cm^{-1}; ^1H NMR (400 MHz) δ: 8.00 (1H, d, *J* = 8.3 Hz, H-6), 7.87 (1H, d, *J* = 8.3 Hz, H-5), 5.17 (1H, s, C<u>H</u>O$_2$), 4.18–4.12 (1H, m, O-C<u>H</u>$_2$), 3.93–3.86 (3H, m, O-C<u>H</u>$_2$), 3.33 (1H, dd, *J* = 3.9, 19.1 Hz, H-α 12), 3.16 (1H, s, H-7), 3.09 (1H, dd, *J* = 13.1, 19.1 Hz, H-β12), 2.14 (3H, s, <u>Me</u>-C2), 2.12 (3H, s, <u>Me</u>-C3), 2.09 (1H, bd, *J* = 13.4 Hz, H-8), 1.68–1.22 (6H, m), 1.10 (3H, s, 11-β-<u>Me</u>), 0.98 (3H, s, 11-α-<u>Me</u>), 0.96 (3H, s, 7a-<u>Me</u>); ^{13}C NMR (100 MHz) δ: 187.4 (C-1), 185.6 (C-4), 144.9 (C-2), 141.8 (C-6a), 141.2 (C-12a), 140.9 (C-3), 134.0 (C-6), 131.6 (C-4a), 129.6 (C-12b), 123.2 (C-5), 103.4 (O-<u>C</u>-O), 65.5 (O-C<u>H</u>$_2$)#, 63.5 (O-C<u>H</u>$_2$)#, 55.5 (C-7), 49.2 (C-11a), 42.1 (C-10), 40.5 (C-8), 34.5 (C-7a), 33.4 (11-α-<u>Me</u>), 33.2 (C-11), 27.5 (C-6), 22.1 (11-β-<u>Me</u>), 18.6 (C-9), 15.3 (7a-<u>Me</u>), 13.4 (3-<u>Me</u>), 12.5 (2-<u>Me</u>). Anal. calcd for $C_{26}H_{32}O_4$: C = 76.44%, H = 7.90%, found: C = 76.12%, H = 8.03%.

(−)-(8*R*,8a*S*,12a*S*)-8-[1,3]Dioxolan-2-yl-8a,12,12-trimethyl-8,8a,9,10,11,12,12a,13-octahydro-pentaphene-5,14-dione (27). Yield: 73%, yellow solid, mp: 188.3–188.7 °C (AcOEt); $[\alpha]_D^{20}$ −106.1 (*c* 4.24); IR (KBr) 1670, 1326, 1303, 1278 cm^{-1}; ^1H NMR (200 MHz) δ: 8.26–8.19 (2H, m, H-1 + H-4), 8.11 (2H, s, H-6 + H-7), 7.79–7.71 (2H, m, H-2 + H-3), 5.20 (1H, s, C<u>H</u>O$_2$), 4.21–4.15

(1H, m, O-CH_2), 3.95–3.84 (3H, m, O-CH_2), 3.46 (1H, dd, J = 4.0, 19.1 Hz, H-α13), 3.23 (1H, dd, J = 12.8, 19.1 Hz, H-β13), 3.20 (1H, s, H-8), 2.10 (1H, bd, J = 12.2 Hz, H-9), 1.70–1.26 (6H, m), 1.14 (3H, s, 12-β-Me), 1.01 (3H, s, 12-α-Me), 1.00 (3H, s, 8a-Me); ^{13}C NMR (50 MHz) δ: 185.4 (C-14), 183.9 (C-5), 142.8 (C-7a), 142.4 (C-13a), 134.8 (C-7), 134.0 (C-2), 133.2 (C-3), 133.0 (C-5a), 132.6 (C-4a), 131.0 (C-13b), 127.2 (C-1), 126.3 (C-4), 124.0 (C-6), 103.4 (O-C-O), 65.5 (O-CH_2)#, 63.6 (O-CH_2)#, 55.5 (C-8), 49.2 (C-12a), 42.1 (C-11), 40.5 (C-9), 34.5 (C-8a), 33.4 (12-α-Me), 33.3 (C-12), 27.9 (C-13), 22.2 (12-β-Me), 18.6 (C-10), 15.3 (8a-Me); analysis: calculated for $C_{28}H_{30}O_4$: C = 78.11%, H = 7.02%, found: C = 77.83%, H = 6.86%.

(−)-(8*R*,8a*S*,12a*S*)-8-[1,3]Dioxolan-2-yl-1,4-dihydroxy-8a,12,12-trimethyl-8,8a,9,10,11,12,12a,13-octahydro-pentaphene-5,14-dione (28). Yield: 54%, orange solid: mp 273.6–274.2 °C (AcOEt); $[\alpha]_D^{16}$ −124.0 (*c* 2.42); IR (KBr) 1617, 1577,1454 cm^{-1}; ^{1}H NMR (200 MHz) δ: 13.23 (1H, s, OH), 12.90 (1H, s, OH), 8.15 (1H, d, J = 8.8 Hz, H-6), 8.11 (1H, d, J = 8.8 Hz, H-7), 7.27 (1H, d, J = 9.3 Hz, H-2), 7.21 (1H, d, J = 9.3 Hz, H-3), 5.20 (1H, s, CHO$_2$), 4.21–4.17 (1H, m, O-CH_2), 3.94–3.89 (3H, m, O-CH_2), 3.49 (1H, dd, J = 4, 0, 19.3 Hz, H-α13), 3.22 (1H, dd, J = 13.0, 19.3 Hz, H-β13), 3.21 (1H, s, H-8), 2.10 (1H, bd, J = 12.4 Hz, H-9), 1.71–1.20 (6H, m), 1.14 (3H, s, 12-β-Me), 1.02 (3H, s, 12-α-Me), 1.00 (3H, s, 8a-Me). ^{13}C NMR (50 MHz) δ: 189.9 (C-14), 187.3 (C-5), 153.3 (C-1), 156.8 (C-4), 143.6 (C-7a)*, 143.4 (C-13a)*, 135.3 (C-7), 132.8 (C-13b), 129.3 (C-2), 127.9 (C-3), 123.7 (C-7), 114.0 (C-14a), 112.6 (C-4a), 103.4 (O-C-O), 65.5 (O-CH_2)#, 63.6 (O-CH_2)#, 55.7 (C-8), 49.1 (C-12a), 42.1 (C-11), 40.5 (C-9), 34.3 (C-8a), 33.4 (12-α-Me), 33.3 (C-12), 28.3 (C-13), 22.2 (12-β-Me), 18.6 (C-10), 15.3 (8a-Me). Anal. calcd for $C_{28}H_{30}O_6$: C = 72.71%, H = 6.54%, found: C = 72.39%, H = 6.38%.

(−)-(8*R*,8a*S*,12a*S*)-8-[1,3]Dioxolan-2-yl-1-hydroxy-8a,12,12-trimethyl-8,8a,9,10,11,12,12a,13-octahydro-pentaphene-5,14-dione (29). The major, more polar compound corresponded to **29** (53 mg, 64%): light orange crystals mp 210.1–210.7 °C (AcOEt); $[\alpha]_D^{16}$ −146.3 (*c* 4.58); IR (KBr) 3442, 1667,1634 cm^{-1}; ^{1}H NMR (200 MHz) δ: 12.97 (1H, s, C1-OH), 8.14 (1H, d, J = 8.5,H-7), 8.07 (1H, d, J = 8.5, H-6), 7.74 (1H, dd, J = 1.2, 7.5 Hz, H-4), 7.60 (1H, dd, J = 7.5, 8.2 Hz, H-3), 7.26 (1H, dd, J = 1.2, 8.2 Hz, H-2), 5.19 (1H, s, CHO$_2$), 4.20–4.15 (1H, m, O-CH_2), 3.94–3.83 (3H, m, O-CH_2), 3.46 (1H, dd, J = 4.0, 19.0 Hz, H-α13), 3.22 (1H, dd, J = 13.0, 19.0 Hz, H-β13), 3.20 (1H, s, H-8), 2.10 (1H, bd, J = 12.2 Hz, H-9), 1.71–1.52 (4H, m, H-10 + H-11), 1.34–1.26 (2H, m, H-12a + H-9), 1.14 (3H, s, 12-β-Me), 1.02 (3H, s, 12-α-Me), 1.00 (3H, s, 8a-Me); ^{13}C NMR (50 MHz) δ: 191.5 (C-14), 183.2 (C-5), 162.3 (C-1), 143.1 (C-13a), 143.0 (C-7a), 135.8 (C-3), 135.5 (C-7), 133.1 (C-4a), 132.8 (C-5a), 130.5 (C-13b), 124.4 (C-2), 124.2 (C-6), 118.5 (C-4), 117.4 (C-14a), 103.4 (O-C-O), 65.5 (O-CH_2)#, 63.6 (O-CH_2)#, 55.6 (C-8), 49.1 (C-12a), 42.1 (C-11), 40.5 (C-9), 34.4 (C-8a), 33.4 (12-α-Me), 33.3 (C-12), 28.3 (C-13), 22.3 (12-β-Me), 18.6 (C-10), 15.3 (8a-Me). Anal. calcd for $C_{28}H_{30}O_5$: C = 75.31%, H = 6.77%, found: C = 75.10%, H = 6.26%.

(−)-(8*R*,8a*S*,12a*S*)-8-[1,3]Dioxolan-2-yl-4-hydroxy-8a,12,12-trimethyl-8,8a,9,10,11,12,12a,13-octahydro-pentaphene-5,14-dione (30). The minor, less polar product corresponded to **30** (18 mg, 22%): light orange crystals, mp 214.0–214.6 °C (AcOEt); $[\alpha]_D^{14}$ −92.6 (*c* 1.08); IR (KBr) 3443, 1664,1635 cm^{-1}; ^{1}H NMR (200 MHz) δ: 12.57 (1H, s, 4-OH), 8.13 (2H, m, H-6 + H7), 7.76 (1H, dd, J = 1.1, 7.6 Hz, H-1), 7.64 (1H, dd, J = 7.6, 8.1 Hz, H-2), 7.23 (1H, dd, J = 1.1, 8.1 Hz, H-3), 5.20 (1H, s, CHO$_2$), 4.21–4.16 (1H, m, O-CH_2), 3.96–3.86 (3H, m, O-CH_2), 3.35 (1H, dd, J = 3.9, 22.3 Hz, H-α13), 3.25–3.22 (1H, m, H-β13), 3.22 (1H, s, H-8), 2.11 (1H, bd, J = 12.1 Hz, H-9), 1.59–1.26 (6H, m), 1.14 (3H, s, 12-β-Me), 1.01 (3H, s, 12-α-Me), 1.00 (3H, s, 8a-Me). ^{13}C NMR (50 MHz) δ: 189.5 (C-5), 185.1 (C-14), 162.2 (C-4), 144.1 (C-7a), 143.3 (C-13a), 137.0 (C-2), 135.6 (C-14a), 135.3 (C-7), 133.0 (C-5a), 131.5 (C-13b), 124.0 (C-6), 123.4 (C-3), 119.7(C-1), 116.0 (C-4a), 103.7 (O-C-O), 65.9 (O-CH_2)#, 64.0 (O-CH_2)#, 56.1 (C-8), 49.6 (C-12a), 42.5 (C-11), 40.9 (C-9), 34.8 (C-8a), 33.8 (12-α-Me), 33.7 (C-12), 28.4 (C-13), 22.6 (12-β-Me), 19.0 (C-10), 15.7 (8a-Me). Anal. calcd for $C_{28}H_{30}O_5$ C = 75.31%, H = 6.77%, found: C = 75.22%, H = 7.02%.

General procedure for the preparation of quinones 1, and 31–33. To a solution of diene **14** (40 mg, 0.20 mmol) in benzene (6 mL), a quinone (0.33 mmol) was added. The resulting yellowish solution was refluxed for 2 h. The solution was allowed to cool to room temperature and DBU (3 drops) was added with stirring. After an additional 15 min, the solvent was evaporated, and the residue was purified by column chromatography, to give the pure quinone.

(+)-(4a*S*,12b*S*)-4,4,12b-Trimethyl-1,2,3,4,4a,5,6,12b-octahydro-benzo[*a*]anthracene-8,11-dione (1). Yield: 46%, yellow oil: $[\alpha]_D^{16}$ +93.18 (*c* 1.395); IR (film) 1739, 1669, 1597 cm^{-1}; ^{1}H NMR (200 MHz) δ: 7.96 (1H, s, H-12), 7.72 (1H, s, H-7), 3.06–2.94 (2H, m, H-6), 2.43 (1H, bd, J = 12.3 Hz, H-1), 2.00–1.21 (8H, m), 1.19 (3H, s, 12b-Me), 0.96 (3H, s, 4-β-Me), 0.94 (3H, s, 4-α-Me); ^{13}C NMR (50 MHz) δ: 185.3 (C-8 + C-11), 156.9 (C-12a), 142.8 (C-6a), 138.9 (C-9), 138.6 (C-10), 129.7 (C-7a), 129.1 (C-11a), 127.4 (C-12), 123.1 (C-7), 49.7 (C-4a), 41.4 (C-3), 38.6 (C-12b), 38.5 (C-1), 33.6 (C-4), 33.2 (C-4-α-Me), 30.7 (C-6), 24.5 (C-4-β-Me), 21.6 (C-12b-Me), 19.0 (C-2), 18.6 (C-5).

(+)-(4a*S*,12b*S*)-4,4,9,10,12b-Pentamethyl-1,2,3,4,4a,5,-6,12b-octahydro-benzo[*a*]anthracene-8,11-dione (31). Yield: 40.5%, pale yellow solid: mp 145–146 °C (AcOEt); $[\alpha]_D^{24}$ +68.97 (*c* 2.61), IR (KBr) 1693, 1658 cm^{-1}, ^{1}H NMR (200 MHz) δ: 7.97 (1H, s, H-12), 7.72 (1H, s, H-7), 3.05–2.93 (2H, m, H-6), 2.43 (1H, bd, J = 12.6 Hz, H-1), 2.15 (6H, s, 10-Me + 9-Me), 2.00–1.23 (8H, m), 1.20 (3H, s, 12b-Me), 0.97 (3H, s, 4-β-Me), 0.95 (3H, s, 4-α-Me); ^{13}C NMR (50 MHz) δ: 185.1 (C-8 + C-11), 156.2 (C-12a), 143.4 (C-9)#, 143.1 (C-10)#, 142.0 (C-6a), 130.0 (C-7a), 129.3 (C-11a), 127.2 (C-12), 122.9 (C-7), 49.8 (C-4a), 41.5 (C-3), 38.6 (C-1), 38.5 (C-12b), 33.6 (C-4), 33.2 (C-4-α-Me), 30.6 (C-6), 24.5 (C-4-β-Me), 21.7 (C-12b-Me), 19.1 (C-2), 18.6 (C-5), 12.9 (9-Me)*, 12.8 (10-Me)*; microanalysis: calculated for $C_{23}H_{28}O_2$, C = 82.10%, H = 8.39%, found: C = 82.44%, H = 8.10%.

(+)-(4a*S*,14b*S*)-4,4,14b-Trimethyl-1,2,3,4,4a,5,6,14b-octahydro-benzo[*a*]naphthacene-8,13-dione (32). Yield: 61%, pale yellow solid: mp 250–251 °C (AcOEt); $[\alpha]_D^{22}$ +62.15 (*c* 1.77); IR (KBr) 1672, 1588, 1330, 1285 cm^{-1}; ^1H NMR (200 MHz) δ: 8.32–8.24 (2H, m, H-9 + H-12), 8.21 (1H, s, H-14), 7.96 (1H, s, H-7), 7.79–7.73 (2H, m, H-10 + H-11), 3.21–2.90 (2H, m, H-6), 2.50 (1H, bd, *J* = 11.8 Hz, H-1), 2.05–1.30 (8H, m), 1.24 (3H, s, 14b-Me), 0.98 (3H, s, 4-β-Me), 0.97 (3H, s, 4-α-Me); ^{13}C NMR (50 MHz) δ: 183.3 (C-8 + C-13), 157.2 (C-14a), 143.1 (C-6a), 133.9 (C-8a)#, 133.84 (C-10)*, 133.79 (C-11)*, 133.7 (C-12a)#, 131.3 (C-7a), 130.6 (C-13a), 128.1 (C-14), 127.1 (C-9)^, 127.0 (C-12)^, 123.8 (C-7), 49.7 (C-4a), 41.5 (C-3), 38.7 (C-14b), 38.6 (C-1), 33.6 (C-4), 33.2 (C-4-α-Me), 30.7 (C-6), 24.5 (C-4-β-Me), 21.7 (C-14b-Me), 19.1 (C-2), 18.6 (C-5); microanalysis: calcd for $C_{25}H_{26}O_2$ C = 83.76%, H = 7.31%; found C = 83.20%, H = 7.41%.

(+) - (4a*S*,14b*S*) - 9,12 - Dihydroxy - 4,4,14b - trimethyl - 1,2,3,4,4a,5,6,14b-octahydro-benzo[*a*]naphthacene-8,13-dione (33). Yield 95%, orange solid: mp 190–191 °C (AcOEt), $[\alpha]_D^{22}$ +95.6 (*c* 2.51), IR (KBr) 1629, 1586, 1456 cm^{-1}; ^1H NMR (400.13 MHz) δ: 12.98 (1H, s, OH), 12.93 (1H, s, OH), 8.23 (1H, s, H-14), 7.91 (1H, s, H-7), 7.24 (2H, s, H-10 + H-11), 3.15 (1H, dd, *J* = 6.5, 17.2 Hz, H-6), 3.01(1H, ddd, *J* = 7.9, 10.7, 17.2 Hz, H-6), 2.49 (1H, bd, *J* = 12.5, H-1), 2.02–1.96 (1H, m, H-5), 1.83–1.68 (3H, m, H-5 + H-2), 1.55–1.48 (2H, m, H-1 + H-3), 1.35 (1H, dd, *J* = 2.4, 12.6 Hz, H-4a), 1.29–1.21 (1H, m, H-3), 1.24 (3H, s, 14b-Me), 0.99 (3H, s, 4-α-Me), 0.97 (3H, s, 4-β-Me); ^{13}C NMR (50 MHz) δ: 187.2 (C-8)*, 187.1 (C-13)*, 157.8 (C-14a), 157.5 (C-9 + C-12), 143.8 (C-6a), 131.1 (C-13a), 130.3 (C-7a), 129.0 (C-10)#, 128.9 (C-11)#, 127.9 (C-7), 123.6 (C-14), 113.0 (C-8a + C-12a), 49.6 (C-4a), 41.4 (C-3), 38.7 (C-14b), 38.5 (C-1), 33.6 (C-4), 33.2 (C-4-α-Me), 30.8 (C-6), 24.6 (C-4-β-Me), 21.7 (C-14b-Me), 19.1 (C-2), 18.6 (C-5); microanalysis: calcd for $C_{25}H_{26}O_4$ C = 76.90%, H = 6.71%; found C = 77.12%, H = 6.89%.

Conclusions

In summary, we described here the synthesis and biological evaluation against *T. cruzi* Tulahuen strain of ten new synthetic naphtho- and anthraquinone sesquiterpene derivatives. Compounds **1** and **25**, demonstrated to be more active than nifurtimox and benznidazole. Compound **31**, a 2,3-dimethyl-1,4-naphthoquinone, and compounds **27** and **32** both of them anthraquinones, were also active against the parasite, but their activity was much lower than the reference substances. The structure and spectra of all new compounds were determined by a full assignment of the NMR spectra, by extensive use of 1D and 2D NMR techniques.

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