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Synthesis of quinone/hydroquinone sesquiterpenes

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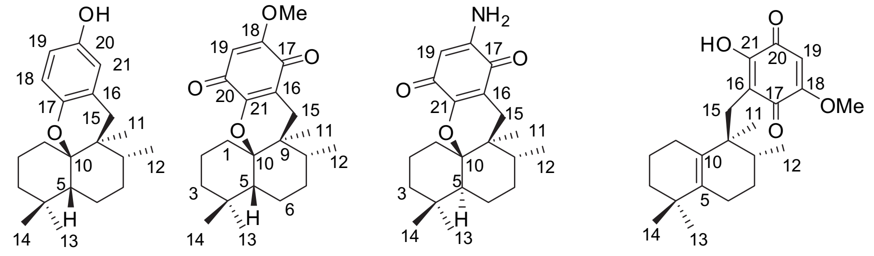
ABSTRACT

ent-Halimic acid has been used in the synthesis of the quinone/hydroquinone sesquiterpenes (−)-aureol, (−)-smenoqualone, (−)-neomamanuthaquinone and in the formal synthesis of (−)-cyclosmenospongine.

1. Introduction

Quinone/hydroquinone sesquiterpenes with drimane or rearranged drimane skeleton are a very wide and diverse group of secondary metabolites of mixed biogenesis with the terpenic unit associated to a quinone or quinol.[1] Those compounds are very interesting not only for their biological activities, but also for the diverse structures that they present.[2,3] Most of them have been isolated from marine sponges, although there are some structures, which have been reported in brown algae and fungi.[4,5,6]

Within this group, the quinone/hydroquinone sesquiterpenes with aureane skeleton (rearranged drimane) (Fig. 1) are the least common in nature, but they present remarkable biological properties such as antiviral and citotoxic[7] against the cellular lines of human lung cancer A549[8] and against Ehrlich cancer cells of mice, haemolytic,[9] antiinflamatory,[10,11] antiproliferative[11] and antimicrobiane.



(-)-aureol
1

(-)-smenoqualone
3

(-)-cyclosmenospongine
4

(-)-neomamanuthaquinone
2

Figure 1.

In the last few years several synthesis and different methodologies for the preparation of substituted or polioxygenated sesquiterpene quinones[12] have been published.

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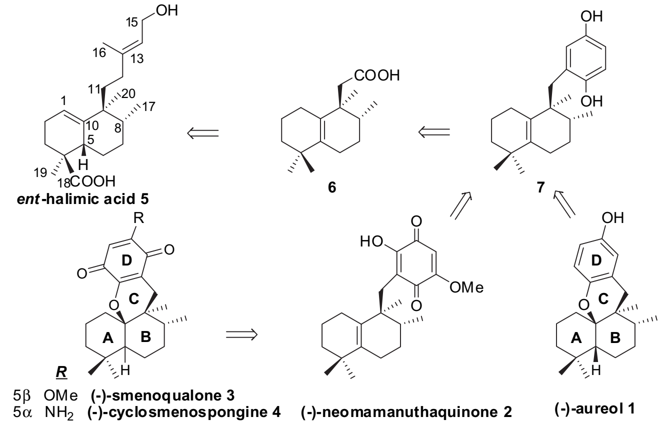
In this paper we describe the synthesis of enantiomers of the natural (+)-neomamanuthaquinone **2**,[10,13] (+)-aureol **1**,[14] (+)-smenoqualone **3**[15] and the formal synthesis of (+)-cyclosmenospongine **4**,[9,13] four quinone/hydroquinone sesquiterpenes with a rearranged drimane skeleton (aureane skeleton, Fig. 1). In the tetracyclic compounds the quinone/quinol unit is attached to the sesquiterpene moiety through a dihydropyran ring with an oxygenated bridge, being cyclosmenospongine the only one with a *trans* decalin junction.

ent-Halimic acid **5**,[16] is a natural diterpene that has been used as starting material in the synthesis of a wide range of natural occurring compounds such as: *ent*-halimanolides,[17] antitumoural sesterterpenolides,[18] chettaphanin I and II,[19] compounds of mixed biogenesis as agelasine C[20] and alkaloid diterpenes: thyersindol C.[21] Its characteristic functionalization and natural abundance turns *ent*-halimic acid into an excellent starting material for the synthesis of the enantiomers of these bioactive compounds, that are interesting targets due to their particular structures and varied biological activities.

2. Results and discussion

The syntheses of those quinone/hydroquinone sesquiterpenes from *ent*-halimic acid **5**, were planned according to the following retrosynthesis, Scheme 1, which is developed by the approach AB→ABD→ABCD.



Scheme 1.

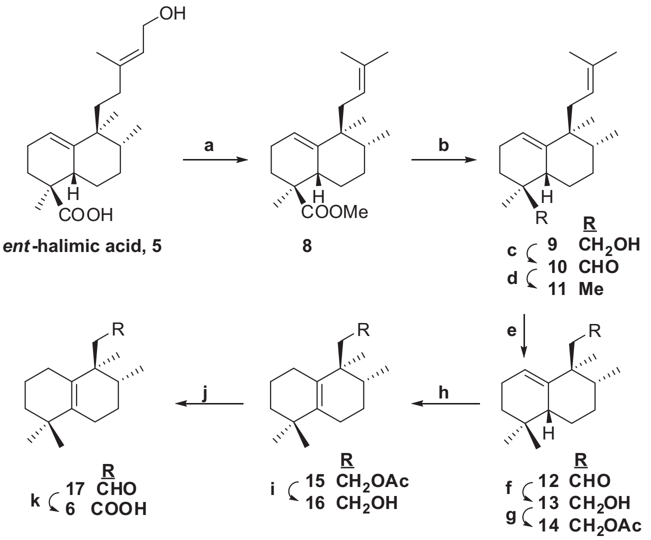
The synthesis of compounds with a quinoid or hydroquinoid moiety can be achieved through an intermediate with the ring D incorporated, for example, compound **7** or an analogue, Scheme 1. This intermediate could be obtained from the tetranorderivative **6**, which would be previously synthesized from *ent*-halimic acid, **5**. The key step, in this sequence is a Barton decarboxylation reaction in presence of benzoquinone.[22]

With **7** in hand, (−)-neomamanuthaquinone **2**, Scheme 1, can be obtained by addition of NaOMe to the quinone ring. This tricyclic sesquiterpene quinone/hydroquinone, **2**, would give access to (−)-smenoqualone **3** and (−)-cyclosmenospongine **4**. On the other hand the ring cyclization of intermediate **7** would provide (−)-aureol **1**.

To begin with, we will comment the elaboration of the key intermediates **6** and **7**, afterwards the synthesis of the target quinone/hydroquinone sesquiterpenes from those intermediates will be described.

2.1. Synthesis of intermediate 6

The synthesis of **6** from *ent*-halimic acid, **5** (Scheme 2) requires reduction at C-18, side chain degradation and double bond isomerization in the bicyclic system.



Scheme 2. Reagents and conditions: (a) Ref. 19; (b) $LiAlH_4$, Et_2O, rt, 35 min, 97%; (c) TPAP, NMO, DCM, rt, 1 h, 97%; (d) $NH_2NH_2 \cdot H_2O$, KOH, diethylene glycol, 175 °C, 17 h, 230 °C, 3 h 30 min, 11, 90%; (e) (1) *m*-CPBA, DCM, rt, 90 min, 98%, (2) H_5IO_6, THF, H_2O, 2 h, rt, 94%; (f) $LiAlH_4$, Et_2O, rt, 50 min, 99%; (g) Ac_2O, Py, rt, 19 h, 99%; (h) HI, C_6H_6, 85 °C, 35 min, 97%; (i) K_2CO_3, MeOH, rt, 2 h, 98%; (j) PDC, DMF, rt, 7 h, 17: 52%, 6: 35%; (k) PDC, DMF, rt, 7 h, 17: 58%, 6: 38%.

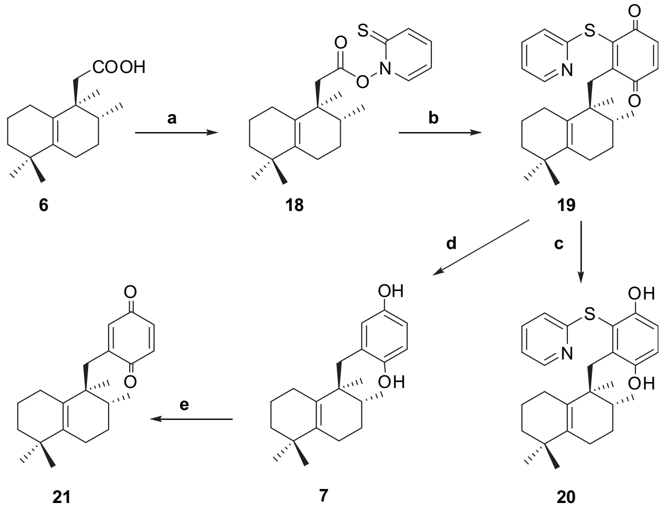
According to the procedure developed in a previous work[19], compound **8** was obtained from *ent*-halimic acid, Scheme 2. Reduction of C-18 to methyl group was achieved in a three steps sequence **9** to **11** in an excellent global yield. The synthesis of the substrate **14**, suitable for the isomerisation of the decalin double bond was carried out in four steps that include chemoselective epoxydation of the side chain double bond in **11**, followed by oxidative cleavage to afford **12**, and finally reduction and acetylation of the hydroxy group at **13**. Reaction of **14** with HI followed by hydrolysis of the acetoxy group afforded the rearranged compound **16** in a very good yield for the two steps. Several conditions were tested for the oxidation of **16** to acid **6**, PDC in DMF[23] being the best one to afford a mixture of aldehyde **17** and acid **6**, which were easily separated. Aldehyde **17** was further oxidised with PDC obtaining in this manner acid **6** in a good global yield. When the time of this reaction was extended only the decomposition of the final compound was achieved.

2.2. Synthesis of intermediate 7

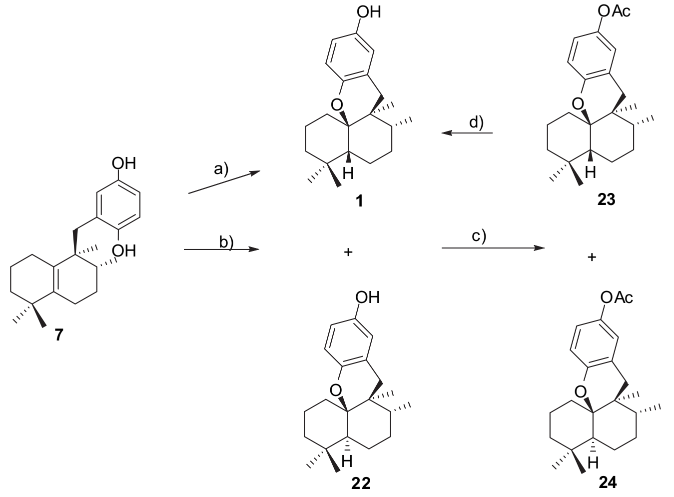
Once intermediate **6** had been obtained, the Barton decarboxylation reaction in the presence of benzoquinone was tested on this substrate. The synthesis of the required photo labile tiohydroxamic ester **18** (Scheme 3) was achieved by reaction of **6** with 2-mercaptopyridine *N*-oxide in the presence of DCC. The reaction was carried out in absence of light due to the photo sensibility of compound **18**.

Light induced decarboxylation (500 W) of **18**, in the presence of benzoquinone, produced quinone **19**.[24] An explanation for **19** formation can be seen in Scheme 4. Reduction of **19** with Ni-Raney, in EtOH/H_2O, afforded **20** while the same reaction in EtOH permitted to obtain hydroquinone **7** whose oxidation with MnO_2 provided **21**, more stable than its precursor hydroquinone (Scheme 3).

The radical mechanism proposed for this reaction is shown in Scheme 4. Derivative **18**, by irradiation (500 W) experiment a decarboxylation to afford radicals **A** and **B**. Radical **A** reacts with *p*-benzoquinone forming radical **C**, that is, coupled with **B**, to provide intermediate **D**. It turns into the corresponding tautomerized form, hydroquinone **20**. The *p*-benzoquinone excess present in the media acts as a redox system for the transformation of the hydroquinone **20** into quinone **19**.



Scheme 3. a) 2-mercaptopyridine *N*-oxide, DCC, DCM, rt, 16 h, darkness; (b) *p*-benzoquinone, DCM, *hν* 500 W, 0 °C, 2 h, 65% from 6; (c) Ni-Raney, EtOH/H_2O, rt, 5 min, 99%; (d) Ni-Raney, EtOH, rt, 5 min, 99%; (e) MnO_2, Et_2O, rt, 30 min, 90%.



Scheme 5. (a) $BF_3\cdot Et_2O$, DCM, −50 °C→−5 °C, 2 h, 60%; (b) *p*-TsOH, C_6H_6, rt, 15 h, reflux 2 h, 1: 67%, 22: 25%; (c) Ac_2O, Py, rt, 15 h, 23: 50%, 24: 49%; (d) $LiAlH_4$, Et_2O, rt, 35 min, 100%.

2.3. Synthesis of (−)-aureol

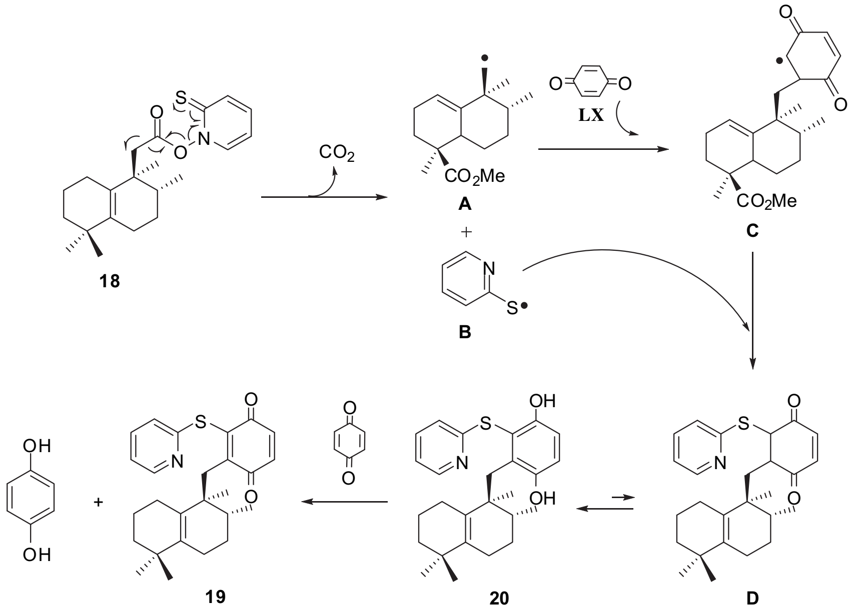
Once obtained hydroquinone **7** the desired compound, **1**, was synthesized as follows (Scheme 5).

Treatment of **7** with $BF_3\cdot Et_2O$ at low temperature exclusively provided **1** with complete stereoseletivity.[25] The spectroscopical properties of **1** were identical with those reported by Faulkner and co-workers for natural (+)-aureol, establishing the configuration at C-5 in compound **1**. The structure of (+)-aureol described by Faulkner and co-workers $[\alpha]_D^{22}$ +65 (*c* 2.0, CCl_4)[14] was corroborated by X-ray of a derivative. The only difference between these structures is the value of the optical rotation, $[\alpha]_D^{22}$ −24.3 (*c* 0.4, $CHCl_3$) for **1**, that is, the enantiomer of (+)-aureol.

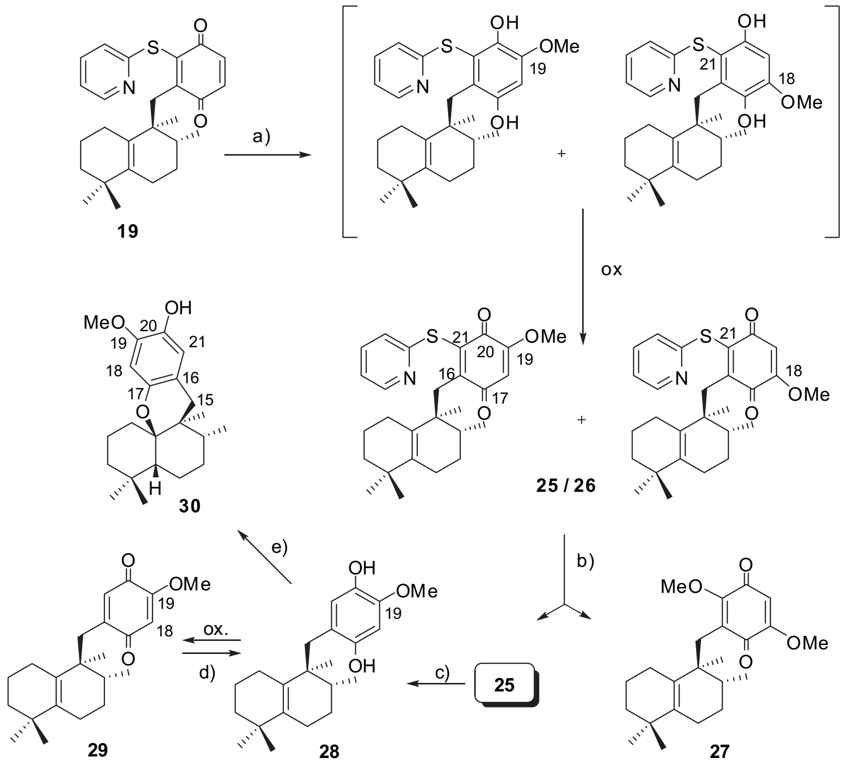
When the cyclization of **7** was performed using *p*-TsOH,[26] instead of $BF_3\cdot Et_2O$, it was obtained a mixture of unstable compounds **1** and **22**, epimers at C-5 in a 67/25 ratio (Scheme 5). Acetylation of the reaction mixture provided the acetylderivatives **23** and **24**, which were easily separated by chromatography. The spectroscopical properties of **23** were identical with those reported for the natural aureol acetate.[14] Reduction of **23** with $LiAlH_4$ yielded again **1**, (−)-aureol, $[\alpha]_D^{22}$ −25.8 (*c* 0.2, $CHCl_3$). Other examples of sesquiterpene quinones that present discrepancy between the optical rotation values in the natural product and in the synthetic one, have been reported.[12b]

2.4. Synthesis of polyoxygenated quinones

With the key intermediate **19** synthesized, we next conduced the synthesis of, (−)-neomamanuthaquinone **2**, (−)-smenoqualone **3** and (−)-cyclosmenosongine **4**, as is shown in Scheme 6. The different substituents in the quinone ring were introduced by successive additions of NaOMe according to the procedure of Theodorakis and co-workers for the synthesis of ilimaquinone.[24]



Scheme 4.



Scheme 6. a) MeONa, THF, −20 °C, 10 min, 25/26 2.5:1, 70%; (b) NaOMe, MeOH, −20 °C→2 °C, 3 h 25: 46%, 27: 27%; (c) Ni-Raney, EtOH, rt, 5 min, 95%; (d) $NaBH_4$, THF, H_2O, rt, 30 min, 97%; (e) $BF_3 \cdot Et_2O$, DCM, −50 °C→−5 °C, 5 h 30 min, 50%.

The first addition of NaOMe to **19** keeping reaction temperature at −20 °C provided a mixture of hydroquinones that were quickly oxidised in contact with air to the corresponding quinones **25**/**26** in a 2.5:1 ratio (Scheme 6). This mixture was not separable by column chromatography.

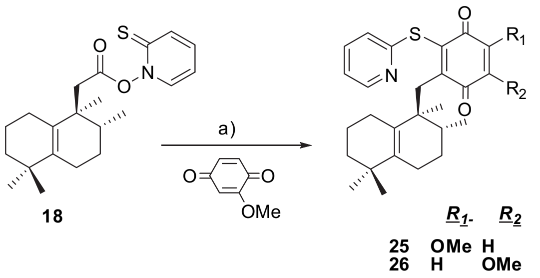
The structure of compounds **25** and **26** was determined by selective transformation of one of them. The mixture of **25**/**26** was treated with NaOMe/MeOH at −20 °C and the reaction was followed by TLC analysis. It was observed that the minor component of the mixture (R_f lower) was transformed progressively, into **27**, while the major component **25** remained unaltered (Scheme 6). The spectroscopical properties of **27**, were coincident with the ones reported for the compound obtained by methylation of the natural compound (+)-neomamanuthaquinone $[\alpha]_D^{22}$ +14.6 (*c* 0.1, $CHCl_3$).[10,27] The optical rotation of **27**, $[\alpha]_D^{22}$ −11.1 (*c* 0.2, $CHCl_3$), shows that this compound is the enantiomer of (+)-neomamanuthaquinone methyl ether.

To determine unequivocally the structure of the major component of the mixture, **25**, the following transformations were carried out, (Scheme 6). Reduction of **25** with Ni-Raney afforded **28** that was quickly oxidised in contact with air yielding the corresponding quinone **29**. New reduction of **29** with $NaBH_4$, provided hydroquinone **28**, which was treated with $BF_3 \cdot Et_2O$ to produce the cyclization compound **30**, 19-methoxyaureol. The structure of **30** was perfectly established by NMR bidimensional experiments HMBC and HMQC, that corroborate the presence of a methoxy group at C-19 in compound **28** and its precursor, **25**.

The HMBC experiment locates the methoxy group at C-19, due to the correlation of the methylene C-15 with one of the aromatic hydrogens, H-21, and the correlation of the other aromatic hydrogen at C-18 with the quaternary carbon C-16.

It is important to underline that to our surprise the ratio of the mixture obtained in the addition of NaOMe to **19** is opposite to the ratio observed by Theodorakis and co-workers in the same reaction made over a similar compound, in the synthesis of ilimaquinone.[24] It might be due to the different conformation of the decalin fragment.

We made an attempt to invert the ratio of the mixture **25**/**26** by irradiation of compound **18**, with a 500 W lamp in presence of methoxy-*p*-benzoquinone, Scheme 7. The result was similar to that obtained by addition of NaOMe to compound **19**, a mixture of **25**/**26** in a 3/1 ratio, Scheme 7.

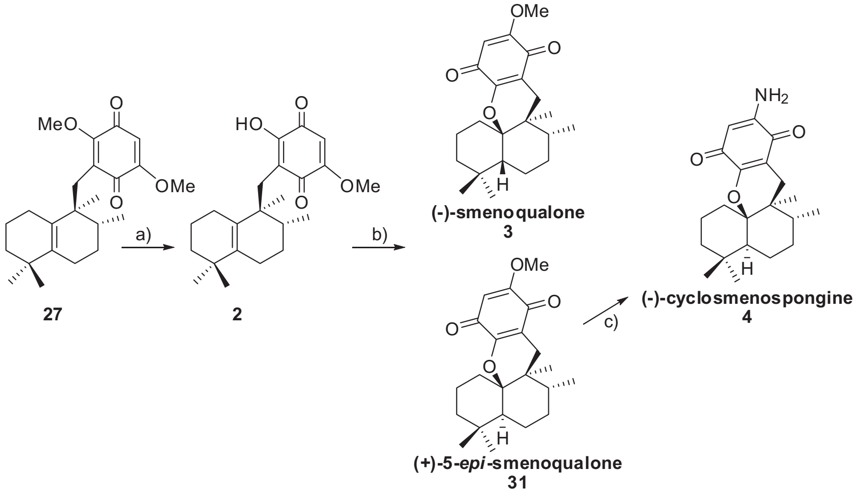


Scheme 7. (a) Methoxy-*p*-benzoquinone, DCM, *hν* 500 W, 0 °C, 2 h, 25: 49%, 26: 17%.

2.4.1. *Synthesis of the enantiomers of the natural products (+)-neomamanuthaquinone, (+)-smenoqualone, (+)-cyclosmenospongine.*

(−)-Neomamanuthaquinone methyl ether **27** is the adequate intermediate for the synthesis of (−)-neomamanuthaquinone **2**, according to the synthetic route shown in Scheme 8.

Selective desmethylation of **27** would provide (−)-neomamanuthaquinone **2**. From this compound the synthesis of (−)-smenoqualone **3** and (−)-cyclosmenospongine **4**, could be easily achieved by a cyclization reaction (Scheme 8).



Scheme 8. (a) $HClO_4$ 60%, THF, rt, 4 h, 70%; (b) *p*-TsOH, C_6H_6, reflux, 30 min, 3: 24%, 31: 20%; (c) Ref. 13.

There are in the literature, numerous precedents of reactions with $HClO_4$ or BCl_3[12b,28] to deprotect the methoxy groups presents in different quinone systems. For that reason compound **27** was treated with $HClO_4$[24,28b,29] to afford **2** $[\alpha]_D^{22}$ −9.1 (*c* 0.1, $CHCl_3$), in a 70% yield, Scheme 8. The spectroscopical properties of **2** were coincident with those reported for the natural (+)-neomamanuthaquinone. In the literature can be found different optical rotation values for the natural compound $[\alpha]_D^{22}$ +3.3 (*c* 0.14, $CHCl_3$),[10] $[\alpha]_D^{22}$ +11 (*c* 0.09, $CHCl_3$).[13] Nevertheless the optical rotation obtained for **2** is in the same order of magnitude that the described values for (+)-neomamanuthaquinone and has opposite sign, therefore it can be concluded that **2** is the enantiomer of the natural compound.

The selectivity observed in the deprotection may be explained by considering the relative stability of the tetrasubstituted enol **A**, formed as a result of the conjugated addition of H_2O at C-21, versus the less substituted one, **B**, arising from the conjugated addition of H_2O at C-18 centre, as can be observed in Figure 2.

Reaction of **2**, with *p*-TsOH in benzene[30] yielded a mixture from which only components **3** $[\alpha]_D^{22}$ −63.5 (*c* 0.1, $CHCl_3$), and **31** $[\alpha]_D^{22}$ +69.3 (*c* 0.1, $CHCl_3$) could be separated in pure form and low yield (Scheme 8).

The spectroscopical properties of **3** were coincident with those described natural (+)-smenoqualone $[\alpha]_D^{22}$ +70 (*c* 1.25×10^{-3}, $CHCl_3$),[15] and the sign of the optical rotation was the opposite, for that reason it can be said that **3** is the enantiomer of natural smenosqualone.

On the other hand the spectroscopical properties of **31**, were identical to those described for (−)-5-*epi*-smenoqualone $[\alpha]_D^{22}$ −75.6 (*c* 0.16, $CHCl_3$),[27] the sign of the optical rotation value indicates that both compounds are enantiomers.

The transformation of 5-*epi*-smenoqualone, into cyclosmenospongine **4** has been described using NH_3 in EtOH[13] therefore the synthesis described in this work constitute a formal synthesis of the enantiomer of sesquiterpene quinone/hydroquinone cyclosmenospongine.

3. Conclusions

ent-Halimic acid is an adequate starting material for the synthesis of quinone/hydroquinone sesquiterpenes (−)-aureol, (−)-smenoqualone, (−)-neomammanuthaquinone and (−)-cyclosmenospongine. The Barton decarboxylation in presence of benzoquinone is the key transformation in these syntheses. The cyclization to get the tetracyclic compound was achieved with *p*-TsOH and in a stereoselective manner with $F_3B\cdot Et_2O$.

4. Experimental

4.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (*J*) are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as *m*/*z* (% rel int.). HRMS were recorded on a VG

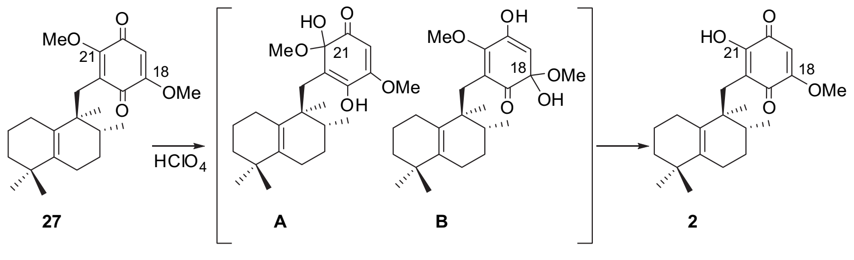


Figure 2.

Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

4.2. Reaction of 8 with LAH to yield 9

A solution of compound **8** (5.74 g, 18.9 mmol) in Et_2O (120 ml) was reduced with LAH (718 mg, 18.9 mmol) at 0 °C for 1 h. Then aqueous Et_2O was added and after filtration, the solvent was evaporated to give a residue, which was purified by silica gel column chromatography (Hex/EtOAc 9/1) to yield **9** (5.05 g, 97%).

4.2.1. 15-Nor-ent-halima-1(10),12-dien-18-ol, ***9***. R_f (Hex/EtOAc 9/1)=0.29; $[\alpha]_D^{22}$ +42.3 (*c* 0.6, $CHCl_3$); IR (film): 3346, 2921, 1453, 1378, 1044, 666; ^1H NMR (200 MHz) δ: 5.30 (1H, m, H-1), 4.93 (1H, m, H-12), 3.43 (1H, d, J=12.0 Hz, H-18$_A$), 3.24 (1H, d, J=12.0 Hz, H-18$_B$), 2.50 (1H, m, H-5), 2.10–1.81 (4H, m), 1.67 (3H, s, Me-14), 1.59 (3H, s, Me-16), 1.39–1.20 (7H, m), 0.87 (3H, s, Me-19), 0.84 (3H, s, Me-20), 0.79 (3H, d, J=6.8 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 142.0 (C-10), 132.9 (C-13), 121.8 (C-12), 119.8 (C-1), 69.5 (C-18), 43.9 (C-9), 38.9 (C-5), 38.1 (C-8), 37.6 (C-11), 36.6 (C-4), 29.5 (C-3), 28.5 (C-7), 26.3 (C-14), 23.6 (C-2), 23.2 (C-20), 22.8 (C-6), 21.1 (C-19), 18.3 (C-16), 15.8 (C-17); EIHRMS: calcd for $C_{19}H_{32}ONa$: 299.2351; found: 299.2345.

4.3. Oxidation of 9 with TPAP to yield 10

To a mixture of **9** (0.80 g, 2.88 mmol), *N*-methylmorpholine *N*-oxide (NMO) (1.18 g, 8.73 mmol) and molecular sieves (700 mg) in anhydrous CH_2Cl_2 (40 ml) under Ar atmosphere, at room temperature was added TPAP (44 mg, 0.13 mmol). The reaction mixture was stirred for 15 min and then filtered on silica gel and Celite® (EtOAc/DCM). Evaporation of the solvent followed by chromatography on silica gel (Hex/EtOAc 9/1) yielded aldehyde **10** (0.77 g, 97%).

4.3.1. 15-Nor-ent-halima-1(10),12-dien-18-al, ***10***. R_f (Hex/EtOAc 9/1)=0.61; IR (film): 2925, 2697, 1726, 1458, 1378, 666; ^1H NMR (200 MHz) δ: 9.37 (1H, s, H-18), 5.32 (1H, m, H-1), 4.98 (1H, t, J=6.2 Hz, H-12), 2.42 (1H, m, H-5), 2.11–1.96 (4H, m), 1.65 (3H, s, Me-14), 1.57 (3H, s, Me-16), 1.39–1.18 (7H, m), 0.93 (3H, s, Me-19), 0.85 (3H, s, Me-20), 0.77 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 207.1 (C-18), 141.4 (C-10), 132.4 (C-13), 121.5 (C-12), 120.2 (C-1), 48.0 (C-4), 43.9 (C-9), 38.4 (C-8), 37.7 (C-11), 36.5 (C-5), 28.9 (C-7), 27.9 (C-3), 26.3 (C-14), 23.2 (C-2), 23.0 (C-20), 22.4 (C-6), 18.3 (C-16), 17.4 (C-19), 15.8 (C-17); EIHRMS: calcd for $C_{19}H_{32}ONa$: 297.2189; found: 297.2171.

4.4. Reduction of 10 to yield 11

To a solution of **10** (0.70 g, 2.57 mmol) in diethylene glycol (23 mL), Hydrazine monohydrate 85% (3.6 mL, 16.7 mmol) and KOH (0.89 g, 15.9 mmol) was added and the mixture was heated at 175 °C for 17 h, then the condenser was removed. After 15 min, the mixture was warmed to 230 °C for 4 h 30 min. Finally, the reaction mixture was allowed to cool to room temperature, quenched with H_2O, 6 M aqueous HCl solution, and extracted with Et_2O. The organic layer washed with water and dried over $NaSO_4$.The solvent was evaporated and the residue, was purified by column chromatography (Hex/EtOAc 95/5) to afford **11** (576 mg, 90%).

4.4.1. 15-Nor-ent-halima-1(10),12-diene, ***11***. R_f (Hex/EtOAc 98/2)= 0.91; $[\alpha]_D^{22}$ +15.0 (*c* 2.4, $CHCl_3$); IR (film): 2924, 1457, 1378, 1327, 1130, 1030, 954, 849; ^1H NMR (200 MHz) δ: 5.30 (1H, m, H-1), 4.97 (1H, t, J=6.8 Hz, H-12), 2.43 (1H, m, H-5), 2.06–1.83 (4H, m), 1.67 (3H, s, Me-14), 1.60 (3H, s, Me-16), 1.39–1.09 (7H, m), 0.87 (6H, s, Me-19 and Me-20), 0.83 (3H, s, Me-18), 0.80 (3H, d, J=6.0 Hz, Me-17); ^{13}C NMR (50 MHz) δ ppm: 142.3 (C-10), 131.9 (C-13), 122.0 (C-12), 119.5 (C-1), 43.9 (C-9), 43.5 (C-5), 38.8 (C-8), 37.8 (C-11), 33.7 (C-3), 31.6 (C-4), 29.5 (C-7), 28.3 (C-19), 26.3 (C-14), 26.1 (C-18), 23.8 (C-6), 23.3 (C-2), 23.2 (C-20), 18.3 (C-16), 15.9 (C-17); EIHRMS: calcd for $C_{19}H_{32}$ ($M+Na^+$): 283.2402; found: 283.2398.

4.5. Reaction of 11 with *m*-CPBA and H_5IO_6 to yield 12

To an ice-cooled solution of **11** (0.21 g, 0.79 mmol) in dry CH_2Cl_2 (7.7 mL) *m*-CPBA (0.15 g, 0.80 mmol) was added. After 1 h, the reaction mixture was diluted with water and extracted with Et_2O. The organic layer was washed successively with aqueous 10%, Na_2SO_3, aqueous 6% $NaHCO_3$ and water and dried over Na_2SO_4. The solvent was evaporated to give the mixture of epoxides derivatives (0.22 g, 98%). This mixture of epoxides (0.22 g, 0.78 mmol) in THF/H_2O (3/1, 11.0 mL) was treated with H_5IO_6 (0.53 g, 2.34 mmol). The reaction mixture was stirred for 2 h at room temperature. Then it was diluted with water and extracted with Et_2O. The organic layer was washed with aqueous 10%, Na_2SO_3, water and dried over Na_2SO_4. The solvent was removed to afford **12** (0.17 g, 94%).

4.5.1. 13,14,15,16-Tetranor-ent-halim-1(10)-en-12-al, ***12***. R_f (Hex/EtOAc 6/4)=0.58; IR (film): 2925, 2705, 1719, 1464, 1381, 1265, 1243, 1046, 740; ^1H NMR (200 MHz) δ: 9.57 (1H, m, H-12), 5.47 (1H, m, H-1), 2.95 (1H, d, J=14.0 Hz, H-11$_A$), 2.12–1.77 (6H, m), 1.65–1.10 (5H, m), 1.09 (3H, s, Me-20), 0.89 (3H, s, Me-19), 0.83 (3H, s, Me-18), 0.80 (3H, d, J=6.6 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 204.5 (C-12), 140.2 (C-10), 121.4 (C-1), 51.8 (C-11), 43.8 (C-5), 42.3 (C-9), 39.3 (C-8), 33.7 (C-3), 31.7 (C-4), 28.3 (C-7), 28.3 (C-19), 25.7 (C-18), 24.1 (C-20), 23.4 (C-6), 23.1 (C-2), 14.9 (C-17).

4.6. Reduction of 12 with LAH to yield 13

A solution of compound **12** (68 mg, 0.29 mmol) in Et_2O (120 ml) was reduced with LAH (13 mg, 0.32 mmol) at 0 °C for 50 min. Then, aqueous Et_2O was added and after filtration, the solvent was evaporated to yield **13** (68 mg, 99%).

4.6.1. 13,14,15,16-Tetranor-ent-halim-1(10)-en-12-ol, ***13***. R_f (Hex/EtOAc 9/1)=0.36; $[\alpha]_D^{22}$ +47.8 (*c* 0.8, $CHCl_3$); IR (film): 3334 (broad), 2925, 1464, 1380, 1364, 1050, 1021; ^1H NMR (200 MHz) δ: 5.36 (1H, m, H-1), 3.54 (2H,m, H-12), 2.30 (1H, m, H-5), 2.09–1.78 (4H, m), 1.60–1.05 (7H, m), 0.96 (3H, s, Me-20), 0.88 (3H, s, Me-19), 0.82 (3H, s, Me-18), 0.78 (3H, d, J=6.8 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 142.1 (C-10), 120.0 (C-1), 60.2 (C-12), 43.5 (C-5), 42.1 (C-9), 41.8 (C-11), 39.6 (C-8), 33.8 (C-3), 31.7 (C-4), 29.2 (C-7), 28.3 (C-19), 25.7 (C-18), 23.6 (C-6), 23.2 (C-2), 23.0 (C-20), 15.4 (C-17); EIHRMS: calcd for $C_{16}H_{28}O$ ($M+Na^+$): 259.2032; found: 259.2043.

4.7. Acetylation of 13 to yield 14

To a solution of **13** (68 mg, 0.29 mmol) in dry pyridine (1.0 mL), Ac_2O (0.5 mL) was added and the mixture was stirred at room temperature overnight. The reaction mixture was then poured into ice water and extracted with EtOAc. The organic layer was washed successively with 2 M aqueous HCl, 6% aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4 and the solvent was evaporated to afford **14** (79 mg, 99%).

4.7.1. 13,14,15,16-Tetranor-ent-halim-1(10)-en-12-ol acetate, ***14***. R_f (Hex/EtOAc 9/1)=0.63; $[\alpha]_D^{22}$ +38.1 (*c* 0.9, $CHCl_3$); IR (film): 2926, 1743, 1457, 1364, 1240, 1031; ^{1}H NMR (200 MHz) δ: 5.34 (1H, t, J=3.2 Hz, H-1), 4.01 (1H, dt, J=10.4, 6.0 Hz, H-12$_A$), 3.86 (1H, dt, J=10.4, 6.0 Hz, H-12$_B$), 2.25 (1H, m, H-5), 2.02 (3H, s, *Me*COO−), 2.01−1.71 (4H, m), 1.58−1.08 (7H, m), 0.95 (3H, s, Me-20), 0.88 (3H, s, Me-19), 0.82 (3H, s, Me-18), 0.79 (3H, d, J=7.4 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 171.4 (Me*C*OO−), 141.0 (C-10), 120.5 (C-1), 62.4 (C-12), 43.5 (C-5), 42.1 (C-9), 39.3 (C-8), 37.2 (C-11), 33.7 (C-3), 31.6 (C-4), 29.2 (C-7), 28.4 (C-19), 25.9 (C-18), 23.6 (C-6), 23.3 (C-2), 23.0 (C-20), 21.4 (*Me*COO−), 15.4 (C-17); EIHRMS: calcd for $C_{18}H_{30}O_2$ (M+Na$^+$): 301.2138; found: 301.2143.

4.8. Isomerization of 14 to yield 15

To a solution of **14** (70 mg, 0.25 mmol) in dry benzene (3.1 mL), was added a solution of 57% HI (20 μL). The reaction mixture was stirred at 85 °C for 35 min. Then, it was allowed to cool to room temperature and was diluted with Et_2O and H_2O. The mixture was extracted with Et_2O and the organic layer was successively washed with 10% $NaHSO_3$, 6% $NaHCO_3$, water and dried over Na_2SO_4. The solvent was removed under vacuum to afford **15** (68 mg, 97%).

4.8.1. 13,14,15,16-Tetranor-ent-halim-5(10)-en-12-ol acetate, ***15****.* R_f (Hex/EtOAc 9/1)=0.63; $[\alpha]_D^{22}$ +69.2 (c 0.8, $CHCl_3$); IR (film): 2926, 1743, 1458, 1364, 1234, 1032; ^{1}H NMR (200 MHz) δ: 4.03 (1H, dt, J=11.0, 7.6 Hz, H-12$_A$), 3.83 (1H, dt, J=10.4, 7.6 Hz, H-12$_B$), 2.02 (3H, s, *Me*COO−), 2.01−1.63 (6H, m), 1.60−1.09 (7H, m), 0.96 (3H, s, Me-20), 0.94 (3H, s, Me-19), 0.86 (3H, d, J=6.6 Hz, Me-17). 0.83 (3H, s, Me-18); ^{13}C NMR (50 MHz) δ: 171.5 (Me*C*OO−), 137.6 (C-5), 131.9 (C-10), 62.3 (C-12), 40.1 (C-9), 40.0 (C-3), 34.6 (C-4), 35.5 (C-11), 34.6 (C-8), 29.2 (C-18), 27.9 (C-19), 27.3 (C-7), 26.1 (C-1), 25.3 (C-6), 21.3 (C-20), 21.3 (*Me*COO−), 20.1 (C-2), 16.4 (C-17); EIHRMS: calcd for $C_{18}H_{30}O_2$ (M+Na$^+$): 301.2138; found: 301.2136.

4.9. Hydrolysis of 15 to yield 16

To a solution of **15** (66 mg, 0.24 mmol) in MeOH (1.9 mL), was added K_2CO_3 (30 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, it was diluted with H_2O and Et_2O. After 15 min stirring the mixture was extracted with Et_2O, and the organic layer was washed with HCl and H_2O and dried over Na_2SO_4. The solvent was evaporated to afford a residue, which was purified by silica gel chromatography (Hex/EtOAc 9/1) to yield **16** (56 mg, 98%).

4.9.1. 13,14,15,16-Tetranor-ent-halim-5(10)-en-12-ol, ***16****.* R_f (Hex/EtOAc 9/1)=0.37; $[\alpha]_D^{22}$ +96.0 (c 1.1, $CHCl_3$); IR (film): 3323 (broad), 2926, 1460, 1380, 1359, 1057, 1026; ^{1}H NMR (200 MHz) δ: 3.53 (2H, m H-12), 1.99−1.80 (4H, m), 1.71−1.12 (9H, m), 0.96 (3H, s, Me-20), 0.93 (3H, s, Me-19), 0.86 (3H, d, J=7.0 Hz, Me-17). 0.82 (3H, s, Me-18); ^{13}C NMR (50 MHz) δ: 137.3 (C-5), 132.7 (C-10), 60.3 (C-12), 40.1 (C-9), 40.1 (C-3), 39.0 (C-11), 34.8 (C-8), 34.7 (C-4), 29.3 (C-18), 27.9 (C-19), 27.4 (C-7), 26.3 (C-1), 25.4 (C-6), 21.4 (C-20), 20.2 (C-2), 16.5 (C-17); EIHRMS: calcd for $C_{16}H_{28}O$ (M+Na$^+$): 259.2069; found: 259.2065.

4.10. Reaction of 16 with PDC to yield 17 and 6

To a solution of **16** (98 mg, 0.42 mmol), in DMF (2.6 mL), PDC (1.04 g, 2.77 mmol) was added. The reaction mixture was stirred at room temperature for 7 h. Then it was cooled at e 0 °C and diluted with water. The resulting mixture was extracted with EtOAc and the organic layer was washed with H_2O and with 10% aq NaOH. The organic layer was washed with H_2O, dried over Na_2SO_4 and the solvent was removed under vacuum to yield **17** (51 mg, 52%). Aqueous layer was treated with aq HCl until pH=1 and then extracted with EtOAc, washed with H_2O and dried over Na_2SO_4. The solvent was evaporated to yield **6** (40 mg, 35%).

4.10.1. 13,14,15,16-Tetranor-ent-halim-5(10)-en-12-al, ***17****.* R_f (Hex/EtOAc 9/1)=0.73; $[\alpha]_D^{22}$ +51.7 (c 0.9, $CHCl_3$); ^{1}H NMR (200 MHz) δ: 9.57 (1H, dd, J=4.0, 1.4 Hz, H-12) 2.48 (1H, dd, J=16.0, 1.4 Hz, H-11$_A$), 2.32 (1H, dd, J=16.0, 1.4 Hz, H-11$_B$), 2.01−1.83 (4H, m), 1.62−1.05 (7H, m), 1.05 (3H, s, Me-20), 0.99 (3H, s, Me-19), 0.91 (3H, s, Me-18), 0.89 (3H, d, J=7.0 Hz, Me-17).

4.10.2. 13,14,15,16-Tetranor-ent-halim-5(10)-en-12-oic acid, ***6****.* R_f (Hex/EtOAc 9/1)=0.40; $[\alpha]_D^{22}$ +42.5 (c 1.0, $CHCl_3$); IR (film): 3100 (broad), 2927, 1705, 1459, 1407, 1381, 1311, 1231, 944; ^{1}H NMR (200 MHz) δ: 2.53 (1H, d, J=14.2 Hz, H-11$_A$), 2.39 (1H, d, J=14.2 Hz, H-11$_B$), 2.01−1.82 (4H, m), 1.62−1.09 (9H, m), 0.97 (3H, s, Me-20), 0.94 (3H, s, Me-19), 0.93 (3H, s, Me-18), 0.84 (3H, d, J=7.0 Hz, Me-17); ^{13}C NMR (50 MHz) δ: 178.1 (C-12), 137.0 (C-5), 131.5 (C-10), 42.2 (C-3), 41.1 (C-9), 39.9 (C-11), 35.0 (C-8), 34.6 (C-4), 28.9 (C-18), 28.2 (C-19), 27.1 (C-7), 26.4 (C-1), 24.1 (C-6), 21.3 (C-20), 20.2 (C-2), 16.4 (C-17); EIHRMS: calcd for $C_{16}H_{26}O_2$ (M+Na$^+$): 273.1825; found: 273.1833.

4.11. Reaction of 17 with PDC to yield 6

To a solution of **17** (0.21 g, 0.76 mmol), in DMF (4.7 mL), PDC (1.89 g, 5.03 mmol) was added. The reaction mixture was stirred at room temperature for 15 h. Then it was cooled at e 0 °C and diluted with water. The resulting mixture was extracted with EtOAc and the organic layer was washed with H_2O and with 10% aq NaOH. The organic layer was washed with H_2O, dried over Na_2SO_4 and the solvent was removed under vacuum to yield **17** (103 mg, 58%) Aqueous layer was treated with aq HCl until pH=1 and then extracted with EtOAc, washed with H_2O and dried over Na_2SO_4. The solvent was evaporated to yield **6** (79 mg, 38%).

4.12. Reaction of 6 with 2-mercaptopyridine *N*-oxide to yield 18

To a solution of acid **6** (115 mg, 0.46 mmol) and 2-mercaptopyridine *N*-oxide (60 mg, 0.46 mmol) in DCM (2.7 mL), was added DCC 1 M in DCM (0.46 mL, 0.46 mmol) under Ar atmosphere. The reaction mixture was stirred at room temperature in the dark for 17 h. Then, the mixture was diluted with DCM, subjected to filtration over cotton to remove the DCU and the filtrate was partitioned with aq satd $NaHCO_3$, and extracted with DCM. The organic layer was collected, dried over Na_2SO_4 and concentrated under vacuum to afford ester **18** (86 mg, 61%).

4.12.1. Compound ***18****.* R_f (Hex/EtOAc 8/2)=0.28; IR (film): 2928, 1810, 1725, 1609, 1527, 1448, 1134, 1042; ^{1}H NMR (200 MHz) δ: 7.69 (1H, dd, J=8.0, 1.8 Hz, H-3′), 7.47 (1H, dd, J=8.0, 1.8 Hz, H-6′), 7.19 (1H, dt, J=8.0, 1.8 Hz, H-4′), 6.61 (1H, dt, J=8.0, 1.8, H-5′), 2.94 (1H, d, J=16.2 Hz, H-11$_A$), 2.80 (1H, d, J=16.2 Hz, H-11$_B$), 2.05−1.90 (4H, m), 1.88−1.51 (2H, m), 1.40−1.05 (5H, m), 1.01 (3H, s, Me-20), 0.98 (3H, s, Me-18), 0.96 (3H, d, J=6.6 Hz, Me-17), 0.94 (3H, s, Me-19).

4.13. Reaction of 18 with *p*-benzoquinona to yield 19

A solution of ester **18** (86 mg, 0.29 mmol) and *p*-benzoquinone (109 mg, 0.87 mmol) in DCM (3.5 mL), was cooled at 0 °C and irradiated with an halogen lamp (500 W) for 2 h. Then, the reaction mixture was concentrated and subjected to silica gel chromatography to afford quinone **19** (85 mg, 70%).

4.13.1. Compound ***19****.* R_f (Hex/EtOAc 8/2)=0.38; $[\alpha]_D^{22}$ −115.7 (c 0.6, $CHCl_3$); IR (film): 3300 (broad), 2929, 2117, 1655, 1577, 1560, 1452, 1418, 1274, 1121; ^{1}H NMR (400 MHz) δ: 8.28 (1H, ddd, $J_{6,5}$=4.8, $J_{6,4}$=2.0, $J_{6,3}$=1.0 Hz, H-6′), 7.54 (1H, dt, $J_{4,5}$ and $J_{4,3}$=8.0, $J_{4,6}$=2.0 Hz, H-4′), 7.31 (1H, dt, $J_{3,4}$=8.0, $J_{3,5}$ and $J_{3,6}$=1.0 Hz, H-3′), 7.02 (1H, ddd, $J_{5,4}$=8.0, $J_{5,6}$=4.8, $J_{5,3}$=1.0 Hz, H-5′), 6.82 (2H, s, H-19, H-20), 3.15 (1H, d, J=12.1 Hz, H-15$_A$), 2.85 (1H, d, J=12.1 Hz, H-15$_B$), 2.20–1.85 (4H, m), 1.71–1.32 (7H, m), 1.04 (3H, s, Me-14), 0.95 (3H, s, Me-13), 0.87 (3H, s, Me-11), 0.79 (3H, d, J=6.9 Hz, Me-12); ^{13}C NMR (100 MHz) δ: 185.3 (C-17), 182.0 (C-20), 157.5 (C-2′), 152.3 (C-21), 149.7 (C-6′), 142.9 (C-16), 137.3 (C-19), 136.8 (C-4′), 136.6 (C-18), 136.1 (C-5), 130.3 (C-10), 122.9 (C-3′), 120.6 (C-5′), 44.3 (C-9), 39.8 (C-15), 39.7 (C-3), 35.9 (C-8), 33.9 (C-4), 29.0 (C-14), 27.8 (C-13), 27.4 (C-1), 25.9 (C-7), 22.8 (C-11), 20.7 (C-6), 19.7 (C-2), 15.6 (C-12); EIHRMS: calcd for $C_{26}H_{31}O_2NS$(M+Na$^+$): 444.1979; found: 444.1968.

4.14. Reaction of 19 with Ni-Raney to yield 20

A solution of **19** (17 mg, 0.04 mmol) in EtOH/H_2O (1 mL), was treated with Ni-Raney (1.2 g, excess). The reaction mixture was stirred for 5 min and then filtered. The solvent was removed under vacuum to afford **20** (17 mg, 99%).

*4.14.1. Compound **20***. IR (film): 3424 (broad), 2929, 1658, 1579, 1561, 1453, 1420, 1379, 1264,1185,759, 738; ^{1}H NMR (200 MHz) δ: 8.43 (1H, ddd, J=4.8, 2.0, 1.0 Hz, H-6′), 7.48 (1H, dt, J=8.0, 2.0 Hz, H-4′), 7.05 (1H, ddd, J=8.0, 4.8, 1.0 Hz, H-5′), 6.96 (1H, d, J=8.8 Hz, H-19), 6.91 (1H, d, J=8.8 Hz, H-18), 6.71 (1H, dt, J=8.0, 1.0 Hz, H-3′), 5.67 (1H, s, –OH), 3.26 (1H, d, J=14.0 Hz, H-15$_A$), 3.00 (1H, d, J=14.0 Hz, H-15$_B$), 2.19–1.98 (4H, m), 1.78–1.23 (7H, m), 1.09 (3H, s, Me-14), 0.99 (6H, s, Me-13 and Me-11), 0.82 (3H, d, J=6.8 Hz, Me-12); EIHRMS: calcd for $C_{26}H_{31}O_2NS$(M+Na$^+$): 446.2124 found: 446.2133.

4.15. Reaction of 19 with Ni-Raney to yield 7

A solution of **19** (17 mg, 0.04 mmol) in EtOH (1 mL), was treated with Ni-Raney (1.4 g, excess). The reaction mixture was stirred for 5 min and then filtered. The solvent was removed under vacuum to yield **7** (12 mg, 99%).

*4.15.1. Compound **7***. R_f (Hex/EtOAc 7/3)=0.41; $[\alpha]_D^{22}$ −13.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz) δ: 6.68 (1H, d, J=8.0 Hz, H-18), 6.64 (1H, d, J=1.2 Hz, H-21), 6.55 (1H, dd, J=8.0, 1.2 Hz, H-19), 4.84 (1H, s ancho, –OH), 4.38 (1H, s ancho, –OH), 2.93 (1H, d, J=12.6 Hz, H-15$_A$) 2.51 (1H, d, J=12.6 Hz, H-15$_B$), 2.06–1.95 (4H, m), 1.90–1.27 (7H, m), 1.05 (3H, s, Me-14), 0.99 (3H, s, Me-13), 0.98 (3H, s, Me-11), 0.83 (3H, d, J=6.6 Hz, Me-12); EIHRMS: calcd for $C_{21}H_{30}O_2$ (M+Na$^+$): 337.2143 found: 337.2150.

4.16. Reaction of 7 with MnO_2 to yield 21

A solution of **7** (5 mg, 0.02 mmol) in Et_2O (0.5 mL), was treated with MnO_2 (7 mg, 0.08 mmol) for 30 min at rt. The reaction mixture was filtered trough Celite®. The filtrate was concentrated to afford **21** (4.5 mg, 90%).

*4.16.1. Compound **21***. R_f (Hex/EtOAc 7/3)=0.51; $[\alpha]_D^{22}$ +8.2 (*c* 0.2, $CHCl_3$); IR (film): 2929, 2119, 1656, 1598, 1522, 1457, 1289, 1068; ^{1}H NMR (200 MHz) δ: 6.70 (3H, m, H-18, H-19, H-21), 2.78 (1H, d, J=16.0 Hz, H-15$_A$), 2.38 (1H, d, J=16.0 Hz, H-15$_B$), 2.05–1.60 (5H, m), 1.43–1.05 (6H, m), 1.00 (3H, s, Me-11), 0.93 (3H, s, Me-14), 0.88 (3H, s, Me-13), 0.81 (3H, d, J=6.6 Hz, Me-12); ^{13}C NMR (50 MHz) δ: 188.1 (C-17), 187.5 (C-20), 147.4 (C-16), 138. 3 (C-5), 137.1 (C-18), 136.2 (C-19), 134.1 (C-21), 131.4 (C-10), 42.0 (C-9), 39.9 (C-3), 34.8 (C-4), 34.3 (C-8), 34.3 (C-15), 28.8 (C-14), 28.1 (C-13), 27.1 (C-1), 26.6 (C-7), 24.4 (C-6), 22.4 (C-11), 20.0 (C-2), 16.6 (C-12); EIHRMS: calcd for $C_{21}H_{28}O_2$ (M+Na$^+$): 335.1987 found: 335.1995.

4.17. Reaction of 7 with $BF_3\cdot Et_2O$ to yield 1

To a stirred solution of **7** (11 mg, 0.03 mmol) in DCM (3.0 mL) at −50 °C was added $BF_3\cdot Et_2O$ (0.015 mL, 0.13 mmol). The resulting mixture was gradually warmed to −5 °C over 2 h 30 min the reaction was quenched with saturated aqueous NH_4Cl at −5 °C and the mixture was extracted with DCM. The combined extracts were washed with saturated NaCl then dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography (Hex/EtOAc 95/5) to yield **1** (6 mg, 60%).

*4.17.1. Compound **1***. R_f (Hex/EtOAc 8/2)=0.38; $[\alpha]_D^{22}$ −24.3 (*c* 0.4, $CHCl_3$); IR (film): 3389, 2932, 1495, 1456, 1384, 1263, 1232, 1186, 981, 954, 808; ^{1}H NMR (400 MHz) δ: 6.60 (1H, d, J=8.6 Hz, H-18), 6.56 (1H, dd, J=8.6, 2.8 Hz, H-19), 6.49 (1H, d, J=2.8 Hz, H-21), 3.37 (1H, d, J=17.1 Hz, H-15$_A$), 1.96 (1H, d, J=17.1 Hz, H-15$_B$), 1.82–1.64 (5H, m), 1.50–1.28 (7H, m), 1.10 (3H, d, J=7.5 Hz, Me-12), 1.06 (3H, s, Me-13), 0.92 (3H, s, Me-11), 0.78 (3H, s, Me-14); ^{13}C NMR (100 MHz) δ: 148.3 (C-20), 145.7 (C-17), 122.2 (C-16), 117.2 (C-18), 115.0 (C-21), 113.9 (C-19), 82.3 (C-10), 44.1 (C-5), 39.3 (C-8), 38.0 (C-9), 37.3 (C-15), 33.9 (C-3), 33.8 (C-4), 31.9 (C-14), 29.8 (C-13), 29.2 (C-1), 27.8 (C-7), 22.2 (C-6), 20.2 (C-11), 18.3 (C-2), 17.3 (C-12); EIHRMS: calcd for $C_{21}H_{30}O_2$ (M+Na$^+$): 337.2143 found: 337.2138.

4.18. Reaction of 7 with *p*-TsOH: 1 and 22

To a solution of **7** (12 mg, 0.04 mmol) in C_6H_6 (30 mL), was added *p*-TsOH (100 mg, 0.51 mmol). After being stirred at room temperature overnight, the reaction mixture was refluxed for 2 h. Then aq 6% $NaHCO_3$ was added. The resulting mixture was extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. The solvent was removed under vacuum to afford a residue, which was chromatographed over silica gel (Hex/EtOAc 8/2) to yield **1** (8 mg, 67%) and **22** (3 mg, 25%).

*4.18.1. Compound **22***. R_f (Hex/EtOAc 7/3)=0.75; $[\alpha]_D^{22}$ −42.0 (*c* 0.1, $CHCl_3$); IR (film): 3389, 2924, 2852, 1494, 1461, 1261, 1222, 1093; ^{1}H NMR (200 MHz) δ: 6.69 (1H, d, J=9.0 Hz, H-18), 6.60 (1H, dd, J=9.0, 3.1 Hz, H-19), 6.49 (1H, d, J=3.1 Hz, H- 21), 4.26 (1H, s ancho, –OH), 2.52 (2H, s, H-15), 2.10–1.95 (3H, m), 1.80–1.36 (9H, m), 1.10 (3H, s, Me-13), 0.96 (6H, s, Me-11 and Me-14), 0.75 (3H, d, J=6.8 Hz, Me-12); EIHRMS: calcd for $C_{22}H_{30}O_3$ (M+Na$^+$): 337.2246; found: 337.2291.

4.19. Reaction of 1/22 with Ac_2O/Py: 23 and 24

To a solution of **1**/**22** (3:1) (11 mg, 0.035 mmol), in dry pyridine (0.5 mL), was added Ac_2O (0.5 mL). The mixture was stirred at room temperature overnight. The reaction mixture was then poured into ice water and extracted with EtOAc. The organic layer was washed successively with 2 M aqueous HCl, 6% aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4 and the solvent was evaporated to afford **23** (9.0 mg, 50%) and **24** (3.3 mg, 49%).

*4.19.1. Compound **23***. R_f (Hex/EtOAc 95/5)=0.50; $[\alpha]_D^{22}$ −27.6 (*c* 0.3, $CHCl_3$); IR (film): 2934, 2872, 1763, 1494, 1466, 1385, 1206, 1140, 1014, 954; ^{1}H NMR (200 MHz) δ: 6.73 (2H, m, H-18, H-19), 6.61 (1H, d, J=1.2 Hz, H-21), 3.45 (1H, d, J=17.4 Hz, H-15$_A$), 2.29 (3H, s, *Me*COO–), 2.25–2.12 (5H, m), 2.00 (1H, d, J=17.4 Hz, H-15$_B$), 1.97–1.65 (7H, m), 1.10 (3H, d, J=7.4 Hz, Me-12), 1.06 (3H, s, Me-13), 0.91 (3H, s, Me-11), 0.79 (3H, s, Me-14); EIHRMS: calcd for $C_{23}H_{32}O_3$(M+Na$^+$): 379.2244; found: 379.2260.

*4.19.2. Compound **24***. R_f (Hex/EtOAc 95/5)=0.47; $[\alpha]_D^{22}$ −6.6 (*c* 0.1, $CHCl_3$); IR (film): 3389, 2933, 1763, 1494, 1459, 1430, 1204, 1171, 1017, 813; ^{1}H NMR (400 MHz), δ: 6.78 (1H, d, *J*=8.0 Hz, H-18), 6.77 (1H, dd, *J*=8.0, 1.2 Hz, H-19), 6.69 (1H, d, *J*=1.2 Hz, H-21), 2.55 (2H, s, H-15), 2.25 (3H, s, *Me*COO–), 1.82–1.64 (5H, m), 1.50–1.28 (7H, m), 1.11 (3H, s, Me-13), 0.91 (6H, s, Me-11 and Me-14), 0.74 (3H, d, *J*=6.8 Hz, Me-12); ^{13}C NMR (100 MHz), δ: 170.0 (MeCOO–), 150.3 (C-17), 143.3 (C-20), 126.1 (C-16), 121.6 (C-21), 120.0 (C-19), 117.3 (C-18), 81.6 (C-10), 45.6 (C-5), 41.9 (C-3), 37.1 (C-9), 33.4 (C-4), 33.4 (C-15), 32.5 (C-14), 31.7 (C-8), 28.3 (C-7), 22.3 (C-13), 21.8 (C-6), 21.0 (*Me*COO–), 21.0 (C-1), 17.8 (C-2), 16.8 (C-11), 16.1 (C-12); EIHRMS: calcd for $C_{23}H_{32}O_3$(M+Na$^+$): 379.2244; found: 379.2229.

4.20. Reduction of 23 with LAH to yield 1

A solution of compound **23** (2 mg, 0.006 mmol) in Et_2O (0.3 mL) was reduced with LAH (2 mg, 0.05 mmol) at 0 °C for 35 min. Then, aqueous Et_2O was added and after filtration, the solvent was evaporated to yield **1** (1.8 mg, 100%).

4.21. Reaction of 19 with NaOMe to yield 25 and 26

To a solution of quinone **19** (24 mg, 0.06 mmol) in THF (1.4 mL) was added drop wise NaOMe/MeOH (2.5 M, 0.12 mL, 0.29 mmol) at −20 °C. The mixture was stirred for 10 min. The reaction mixture was treated with aq satd NH_4Cl at −20 °C and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. The solvent was removed under vacuum to afford a residue, which contains **25**/**26** (21 mg, 80%). The residue was chromatographed over silica gel (Hex/EtOAc 95/5) to yield **25** (13 mg, 45%), and **26** (5 mg, 21%).

*4.21.1. Compound **25**.* R_f (Hex/EtOAc 7/3)=0.39; $[\alpha]_D^{22}$ −70.4 (*c* 0.3, $CHCl_3$); IR (film): 3391, 2927, 2852, 1630, 1560, 1511, 1457, 1220, 1121, 1090; ^{1}H NMR (400 MHz, C_6H_6) δ: 8.09 (1H, ddd, *J*=4.8, 2.0, 1.0 Hz, H-6′), 6.99 (1H, dt, *J*=8.0, 1.0 Hz, H-3′), 6.77 (1H, dt, *J*=8.0, 2.0 Hz, H-4′), 6.32 (1H, ddd, *J*=8.0 4.8, 1.0 Hz, H-5′), 5.64 (1H, s, H-18), 3.45 (1H, d, *J*=12.0 Hz, H-15$_A$), 3.13 (1H, d, *J*=12.0 Hz, H-15$_B$), 2.79 (3H, s, –OMe), 2.01–1.60 (4H, m), 1.55–1.28 (7H, m), 1.24 (3H, s, Me-14), 1.14 (3H, s, Me-11), 1.05 (3H, s, Me-13), 0.93 (3H, d, *J*=7.7 Hz, Me-12); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J*=4.8 Hz, H-6′), 7.52 (1H, t, *J*=8.0 Hz, H-4′), 7.30 (1H, d, *J*=8.0 Hz, H-3′), 7.02 (1H, dd, *J*=8.0, 4.8 Hz, H-5′), 5.98 (1H, s, H-18), 3.82 (3H, s, –OMe), 3.15 (1H, d, *J*=12.0 Hz, H-15$_A$), 2.88 (1H, d, *J*=12.0 Hz, H-15$_B$), 2.20–1.80 (4H, m), 1.75–1.10 (7H, m), 1.05 (3H, s, Me-14), 0.96 (3H, s, Me-11), 0.88 (3H, s, Me-13), 0.79 (3H, d, *J*=7.7 Hz, Me-12); ^{13}C NMR (100 MHz, C_6H_6) δ: 185.1 (C-17), 176.5 (C-20), 159.5 (C-19), 158.0 (C-2′), 152.7 (C-21), 149.5 (C-6′), 140.6 (C-16), 136.0 (C-4′), 135.9 (C-5), 131.0 (C-10), 122.5 (C-3′), 119.9 (C-5′), 107.5 (C-18), 54.8 (–OMe), 44.4 (C-9), 39.9 (C-3), 39.7 (C-15), 35.9 (C-8), 34.3 (C-4), 28.9 (C-14), 27.8 (C-13), 27.6 (C-1), 26.1 (C-7), 22.7 (C-11), 20.9 (C-6), 19.9 (C-2), 15.6 (C-12); EIHRMS: calcd for $C_{27}H_{33}NO_3S$ (M+Na$^+$): 474.2073; found: 474. 2077.

*4.21.2. Compound **26**.* R_f (Hex/EtOAc 7/3)=0.34; IR (film): 3390, 2927, 2852, 1630, 1563, 1458, 1220, 1090; ^{1}H NMR (400 MHz, C_6H_6) δ: 8.22 (1H, ddd, *J*=4.8, 2.0, 1.0 Hz, H-6′), 7.06 (1H, dt, *J*=8.0, 1.0 Hz, H-3′), 6.83 (1H, dt, *J*=8.0, 2.0 Hz, H-4′), 6.39 (1H, ddd, *J*=8.0, 4.8, 1.0 Hz, H-5′), 5.67 (1H, s, H-19), 3.42 (1H, d, *J*=12.0 Hz, H-15$_A$), 3.09 (1H, d, *J*=12.0 Hz, H-15$_B$), 2.80 (3H, s, –OMe), 2.01–1.60 (4H, m), 1.55–1.28 (7H, m), 1.21 (3H, s, Me-14), 1.09 (3H, s, Me-11), 1.03 (3H, s, Me-13), 0.83 (3H, d, *J*=7.6 Hz, Me-12); ^{13}C NMR (100 MHz, C_6H_6) δ ppm: 181.1 (C-17), 180.9 (C-20), 158.8 (C-18), 158.7 (C-2′), 150.9 (C-21), 149.9 (C-6′), 144.9 (C-16), 136.0 (C-4′), 135.8 (C-5), 130.7 (C-10), 122.5 (C-3′), 119.9 (C-5′), 108.3 (C-19), 54.8 (–OMe), 44.0 (C-9), 39.9 (C-3), 39.6 (C-15), 36.0 (C-8), 34.3 (C-4), 28.9 (C-14), 27.8 (C-13), 27.6 (C-1), 26.0 (C-7), 22.7 (C-11), 20.9 (C-6), 19.8 (C-2), 15.5 (C-12); EIHRMS: calcd for $C_{27}H_{33}NO_3S$(M+Na$^+$): 474.2073; found: 474. 2090.

4.22. Reaction of 25/26 with NaOMe to yield 25 and 27

To a solution of **25**/**26** (9 mg, 0.02 mmol), in THF (0.8 mL), was added drop wise NaOMe/MeOH (3.8 M, 0.02 mL, 0.06 mmol) at −20 °C. The reaction mixture was stirred and slowly warmed up to 2 °C over 3 h. The reaction mixture was quenched with aq sat NH_4Cl and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed over silica gel (Hex/EtOAc 98/2) to afford **27** (2 mg, 27%) and **25** (4 mg, 46%).

*4.22.1. Neomamanuthaquinone methyl ether, **27**.* R_f (Hex/EtOAc 7/3)=0.51; ^{1}H NMR (200 MHz) δ: 5.72 (1H, s, H-19), 4.03 (3H, s, –OMe), 3.81 (3H, s, –OMe), 2.72 (1H, d, *J*=10.1 Hz, H-15$_A$), 2.55 (1H, d, *J*=10.1 Hz, H-15$_B$), 2.16–1.82 (5H, m), 1.80–1.22 (6H, m), 1.01 (3H, s, Me-11), 0.96 (3H, s, Me-14), 0.79 (3H, s, Me-13), 0.77 (3H, d, *J*=6.6 Hz, Me-12); ^{13}C NMR (50 MHz) δ: 183.6 (C-20), 183.0 (C-17), 159.0 (C-18), 157.0 (C-21), 135.0 (C-5), 131.3 (C-10), 129.1 (C-16), 105.2 (C-19), 61.0 (–OMe), 56.4 (–OMe), 42.6 (C-9), 40.0 (C-3), 34.5 (C-4), 34.5 (C-8), 32.2 (C-15), 29.0 (C-14), 28.0 (C-13), 26.5 (C-7), 25.7 (C-1), 22.0 (C-11), 20.6 (C-6), 20.0 (C-2), 15.4 (C-12); EIHRMS: calcd for $C_{27}H_{33}NO_3S$ (M+Na$^+$): 395.2343; found: 395.2349.

4.23. Reaction of 25 with Ni-Raney to yield 29

A solution of **25** (5 mg, 0.11 mmol) in EtOH (1.3 mL), was treated with Ni-Raney (1 g, excess) for 5 min. The reaction mixture was then filtered, the filtrate was concentrated to afford **29** (3.6 mg, 95%).

*4.23.1. Compound **29**.* R_f (Hex/EtOAc 6/4)=0.68; $[\alpha]_D^{22}$ +11.5 (*c* 0.2, $CHCl_3$); IR (film): 2925, 2853, 1726, 1673, 1648, 1603, 1460, 1216; ^{1}H NMR (200 MHz) δ: 6.61 (1H, s, H-21), 5.91 (1H, s, H-18), 3.80 (3H, s, –OMe), 2.80 (1H, d, *J*=16.2 Hz, H-15$_A$), 2.39 (1H, d, *J*=16.2 Hz, H-15$_B$), 2.09–1.97 (5H, m), 1.82–1.43 (6H, m), 1.00 (3H, s, Me-11), 0.99 (3H, s, Me-14), 0.88 (3H, s, Me-13), 0.81 (3H, d, *J*=6.6 Hz, Me-12); ^{13}C NMR (50 MHz) δ: 187.9 (C-17), 182.4 (C-20), 158.4 (C-19), 148.3 (C-16), 138.3 (C-5), 132.7 (C-21), 131.1 (C-10), 107.9 (C-18), 56.3 (–OMe), 41.9 (C-9), 39.9 (C-3), 34.4 (C-8), 33.7 (C-15), 33.7 (C-4), 28.7 (C-14), 28.2 (C-13), 27.1 (C-1), 26.6 (C-7), 24.3 (C-6), 22.4 (C-11), 20.0 (C-2), 16.6 (C-12); EIHRMS: calcd for $C_{22}H_{30}O_3$(M+Na$^+$): 365.2087; found: 365.2091.

4.24. Reaction of 29 with $NaBH_4$ to yield 28

To an ice-cooled solution of **29** (35 mg, 0.10 mmol) in THF/H_2O (2.8/0.3 mL), $NaBH_4$ (8 mg, 0.20 mmol) was added. After being stirred at room temperature for 3 h, the reaction mixture was recooled to 0 °C and quenched with a few drops of 2 M aqueous HCl solution, diluted with EtOAc and water and extracted with EtOAc. The organic layer was washed with water. Evaporation of the dried extract gave **28** (34 mg, 97%).

4.25. Reaction of 28 with $BF_3 \cdot Et_2O$ to yield 30

To a stirred solution of **28** (34 mg, 0.10 mmol) in DCM (9.0 mL) at −50 °C was added $BF_3 \cdot Et_2O$ (0.07 mL, 0.51 mmol). The resulting mixture was gradually warmed to −5 °C over 5 h 30 min the reaction was quenched with saturated aqueous NH_4Cl at −5 °C and the mixture was extracted with DCM. The combined extracts were washed with saturated NaCl then dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography (Hex/EtOAc 95/5) to yield **30** (30 mg, 50%).

*4.25.1. 19-Methoxyaureol, **30**.* R_f (Hex/EtOAc 7/3)=0.70; $[\alpha]_D^{22}$ −32.1 (*c* 0.4, $CHCl_3$); IR (film): 3424, 2958, 2872, 1630, 1510, 1447, 1261, 1234, 1117, 956; ^{1}H NMR (400 MHz) δ: 6.54 (1H, s, H-21), 6.29 (1H, s, H-18), 3.82 (3H, s, −OMe), 3.31 (1H, d, *J*=17.0 Hz, H-15_A), 1.90 (1H, d, *J*=17.0 Hz, H-15_B), 1.82−1.64 (5H, m), 1.50−1.28 (7H, m), 1.10 (3H, d, *J*=7.5 Hz, Me-12) 1.08 (3H, s, Me-14), 0.92 (3H, s, Me-11), 0.79 (3H, s, Me-13); ^{13}C NMR (100 MHz) δ: 145.3 (C-19), 144.8 (C-17), 138.8 (C-20), 113.7 (C-21), 112.9 (C-16), 100.0 (C-18), 82.4 (C-10), 56.0 (−OMe), 43.9 (C-5), 39.3 (C-8), 38.1 (C-9), 36.7 (C-15), 33.8 (C-3), 33.8 (C-4), 31.9 (C-14), 29.9 (C-13), 29.2 (C-1), 27.9 (C-7), 22.2 (C-6), 20.1 (C-11), 18.3 (C-2), 17.3 (C-12); EIHRMS: calcd for $C_{22}H_{32}O_3$($M+Na^+$): 367.2244; found: 367.2263.

4.26. Reaction of 18 with methoxy-*p*-benzoquinona: 25 and 26

A solution of ester **18** (37 mg, 0.1 mmol) and methoxy-*p*-benzoquinone (41.4 mg, 0.3 mmol) in DCM (2.3 mL) was cooled at 0 °C and irradiated with a lamp (500 W) for 2 h. The reaction mixture was concentrated and chromatographed over 5 g of silica gel (Hex/EtOAc 95/5) to yield **25** (26 mg, 49%) and **26** (9 mg, 17%).

4.27. Reaction of 27 with $HClO_4$ to yield 2

To a solution of **27** (10 mg, 0.03 mmol) in THF (1 mL), 0.5 mL of 60% $HClO_4$ were added. The reaction mixture was stirred at room temperature for 4 h. Then the reaction mixture was diluted with water and EtOAc. The resulting mixture was extracted with EtOAc. The organic layer was washed with aq 6% $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated to yield **2** (6 mg, 70%).

*4.27.1. (−)-Neomamanuthaquinone, **2**.* R_f (Hex/EtOAc 7/3)=0.30; $[\alpha]_D^{22}$ −9.1 (*c* 0.1, $CHCl_3$); ^{1}H NMR (200 MHz) δ: 5.85 (1H, s, H-19), 3.86 (3H, s, −OMe), 2.70 (1H, d, *J*=13.1 Hz, H-15_A), 2.54 (1H, d, *J*=13.1 Hz, H-15_B), 2.10−1.80 (5H, m), 1.55−1.32 (6H, m), 0.97 (3H, s, Me-11), 0.93 (3H, s, Me-14), 0.81 (3H, s, Me-13), 0.76 (3H, d, *J*=6.7 Hz, Me-12); ^{13}C NMR (50 MHz) δ: 183.0 (C-20), 182.5 (C-17), 161.5 (C-18), 153.5 (C-21), 135.0 (C-5), 131.5 (C-10), 118.0 (C-16), 105.0 (C-19), 56.4 (−OMe), 43.0 (C-9), 40.0 (C-3), 34.9 (C-8), 34.5 (C-4), 32.4 (C-15), 29.7 (C-14), 28.0 (C-13), 25.6 (C-1), 25.5 (C-7), 22.0 (C-11), 21.5 (C-6), 20.0 (C-2), 15.3 (C-12); EIHRMS: calcd for $C_{22}H_{30}O_4$($M+Na^+$): 381.2034; found: 581.2022.

4.28. Reaction of 2 with *p*-TsOH to yield 3 and 31

A mixture of **2** (5 mg, 0.014 mmol) and *p*-TsOH (12 mg, 0.07 mmol) in dry benzene (1.6 mL) was refluxed for 30 min. Then it was quenched with aq 6% $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4. The solvent was removed under vacuum to afford a residue, which was purified by column chromatography over silica gel (Hex/EtOAc 98/2) to yield **3** (1.2 mg, 24%) and **31** (1 mg, 20%).

*4.28.1. (−)-Smenoqualone, **3**.* $[\alpha]_D^{22}$ −63.5 (*c* 0.1, $CHCl_3$); IR (film): 2932, 1663, 1648, 1605, 1495, 1384, 1221, 1186; ^{1}H NMR (200 MHz) δ: 5.70 (1H, s, H-19), 3.78 (3H, s, −OMe), 2.80 (1H, d, *J*=18.6 Hz, H-15_A), 1.94 (1H, d, *J*=18.6 Hz, H-15_B), 1.82−1.64 (5H, m), 1.50−1.28 (7H, m), 1.07 (3H, d, *J*=7.6 Hz, Me-12), 0.99 (3H, s, Me-13), 0.84 (3H, s, Me-11), 0.80 (3H, s, Me-14); ^{13}C NMR (50 MHz) δ: 181.4 (C-17), 181.4 (C-20), 159.5 (C-18), 151.0 (C-21), 115.2 (C-16), 104.7 (C-19), 87.8 (C-10), 56.1 (-OMe), 45.0 (C-5), 39.0 (C-8), 38.0 (C-9), 33.6 (C-4), 33.4 (C-3), 32.0 (C-14), 30.6 (C-15), 29.6 (C-13), 29.0 (C-1), 27.7 (C-7), 22.5 (C-6), 20.0 (C-11), 18.3 (C-2), 17.0 (C-12); EIHRMS: calcd for $C_{22}H_{30}O_4$ ($M+Na^+$): 381.2042; found: 381.2049.

*4.28.2. (+)-5-epi-Smenoqualone, **31**.* $[\alpha]_D^{22}$ +69.3 (*c* 0.1, $CHCl_3$); IR (film): 2932, 1664, 1648, 1600, 1495, 1384, 1219, 981; ^{1}H NMR (200 MHz) δ: 5.74 (1H, s, H-19), 3.80 (3H, s, −OMe), 2.57 (1H, d, *J*=20.0 Hz, H-15_A), 2.00 (1H, d, *J*=20.0 Hz, H-15_B), 1.98−1.36 (12H, m), 1.17 (3H, s, Me-13), 0.96 (3H, s, Me-14), 0.94 (3H, s, Me-11), 0.77 (3H, d, *J*=6.0 Hz, Me-12); ^{13}C NMR (50 MHz) δ: 181.5 (C-17), 181.5 (C-20), 159.5 (C-18), 152.5 (C-21), 115.1 (C-16), 105.0 (C-19), 86.5 (C-10), 56.4 (−OMe), 45.5 (C-5), 41.7 (C-3), 37.0 (C-9), 33.5 (C-4), 32.5 (C-14), 32.4 (C-8), 30.3 (C-15), 29.5 (C-7), 26.7 (C-1), 22.3 (C-13), 22.0 (C-6), 17.8 (C-2), 17.0 (C-11), 16.4 (C-12); EIHRMS: calcd for $C_{22}H_{30}O_4$ ($M+Na^+$): 381.2042; found: 381.2051.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.08.038.

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