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Synthesis of novel antitumoural analogues of dysidiolide from *ent*-halimic acid

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Abstract—Several sesterterpenolides analogues of dysidiolide have been synthesized and their in vitro antitumoural activity against human HeLa, A549, HT-29 and HL-60 carcinoma cells is presented. The proliferation inhibition data showed a significant antitumour activity of the compounds **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5**, inhibiting proliferation of distinct cancer cell types with an IC_{50} in the low micromolar range.

1. Introduction

The sesterterpenoids are metabolites many isolated from spongia species, as *Thorectidae* family which includes the genera: *Luffariella*, *Cacospongia*, *Fasciospongia* and *Thorecta*. A considerable number of them possess in their structures butenolides and hydroxybutenolides being these groups associated to their biological activity.

Manoalide[1] and luffolide[2] are the first sesterterpenolides isolated from *Luffariella* species that present anti-inflammatory activity and are inhibitors of phospholipase A_2.[3] A number of sesterterpenolides with anti-microbial, ictiotoxic and anti-feedant activity have been characterized.[4] The total synthesis of some of them, such as luffolide[5] and cacospongionolide F,[6] has been reported recently (Fig. 1).

The sesterterpene dysidiolide, with a γ-hydroxybutenolide group, has been one of the more attractive compounds during the last years without any doubt (Fig. 1). It was isolated by Gunasekera et al. in 1996, from the Caribbean sponge *Dysidea etherea* de Laubenfels.[7] Its structure was determined on the basis of spectroscopic data and corroborated via X-ray crystallography. Dysidiolide is the first known natural inhibitor of phosphatase enzyme cdc25A ($IC_{50} \approx 9.4$ μM) and also its equivalent cdc25B ($IC_{50} \approx 87$ μM), causing stage specific arrest of the cell cycle at the GI/S transition and loss of the G2/M peak.[8,9] More recently there have been proofs that dysidiolide inhibits the growth of A-549 human lung carcinoma and P388 murine leukaemia cell lines with low IC_{50} values.[6]

Because of its new and unusual structure and its biological activity, dysidiolide has attracted considerable attention from a number of chemists, biologists and pharmacologists.[10] Several total syntheses have been reported by now, of the natural product (−)-dysidiolide,[11–15] its enantiomer (+)-dysidiolide[16,17] and its racemic (±)-dysidiolide.[18–20] Additional syntheses of several analogues of dysidiolide have been published, some of them through solid-phase synthesis.[21]

We have previously synthesised from *ent*-halimic acid,[22] in 2002, compounds **I** and **II**[23] corresponding to the original structures proposed for cladocorans A and B, which are two sesterterpenolides isolated in 1998,[24] analogues of dysidiolide (Fig. 1). Finally in 2003 the correct structures for the natural products cladocorans A and B were established by synthesis[25] (Fig. 1). Sesterterpenolides **III**

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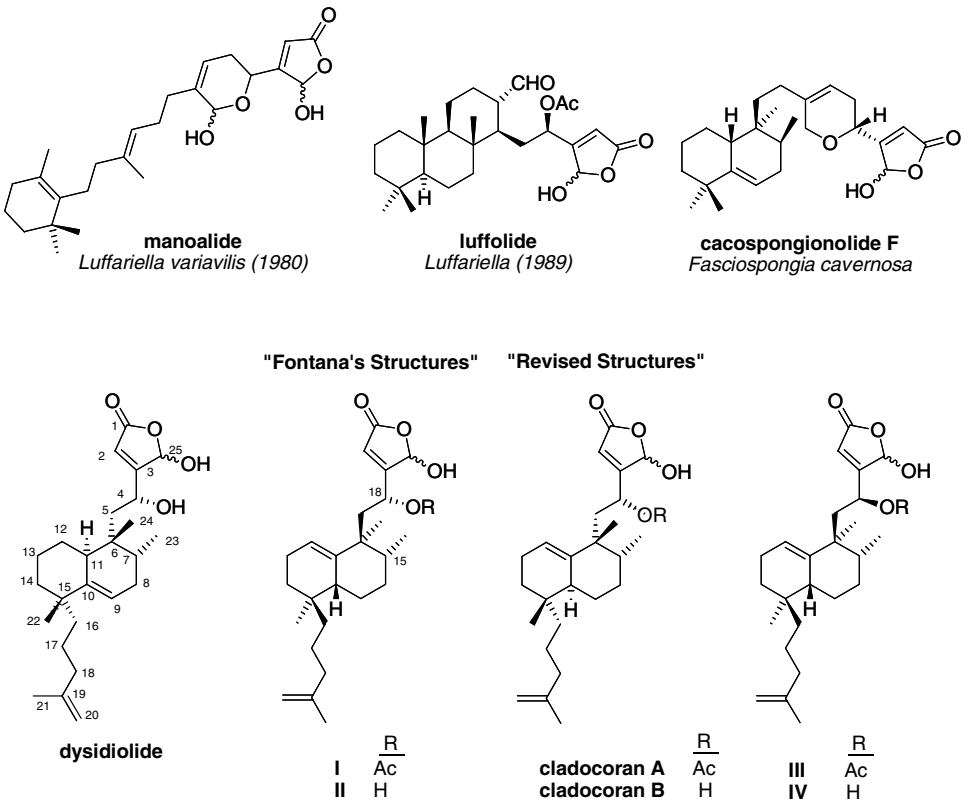


Figure 1.

and **IV**, which are C-18 epimers of **I** and **II**, were also synthesised in the same work. The biological assays carried out with **II**, **III** and **IV**show that these lactones inhibit cellular proliferation ($IC_{50} \approx 2\ \mu M$) of a number of human leukaemic and solid tumour cell lines.[26] These encouraging results prompted us to carry out the synthesis of new analogues of dysidiolide and a structure activity relationship study.

Basically we pretend to change the position of the side chains in the bicyclic system as well as functionalization of the side chains and the bicyclic system. Subsequently our objectives are the synthesis of sesterterpenolides analogues of dysidiolide **1**–**6** Scheme 1.

2. Results and discussion

For preparation of analogues **1**–**6** we use of *ent*-halimic acid methyl ester **7**[22] as starting material as shown in the following retrosynthetic scheme (Scheme 1). *Ent*-halimic acid has been used before for the synthesis of other bioactive compounds.[22]

Methylketone **8** appears as the key intermediate for the synthesis of derivatives **9** and **16**, which already possess the elaborated north chain, the later compound is obtained through the hydroxyderivative **14**. From **9** and **16** the south chain is elongated in one carbon in order to get aldehydes **23**, **26** and the ketone **29**. Finally from **23**, **26** and **29** we proceeded to introduce the γ-hydroxybutenolide moiety in order to obtain the sesterterpenolides **1**–**5**. Synthesis of lactone **6** will be achieved using a similar strategy to that employed for the rest of derivatives (Scheme 1), elaborating first of all the north chain until intermediate **18** and then the south chain through ketone **35**.

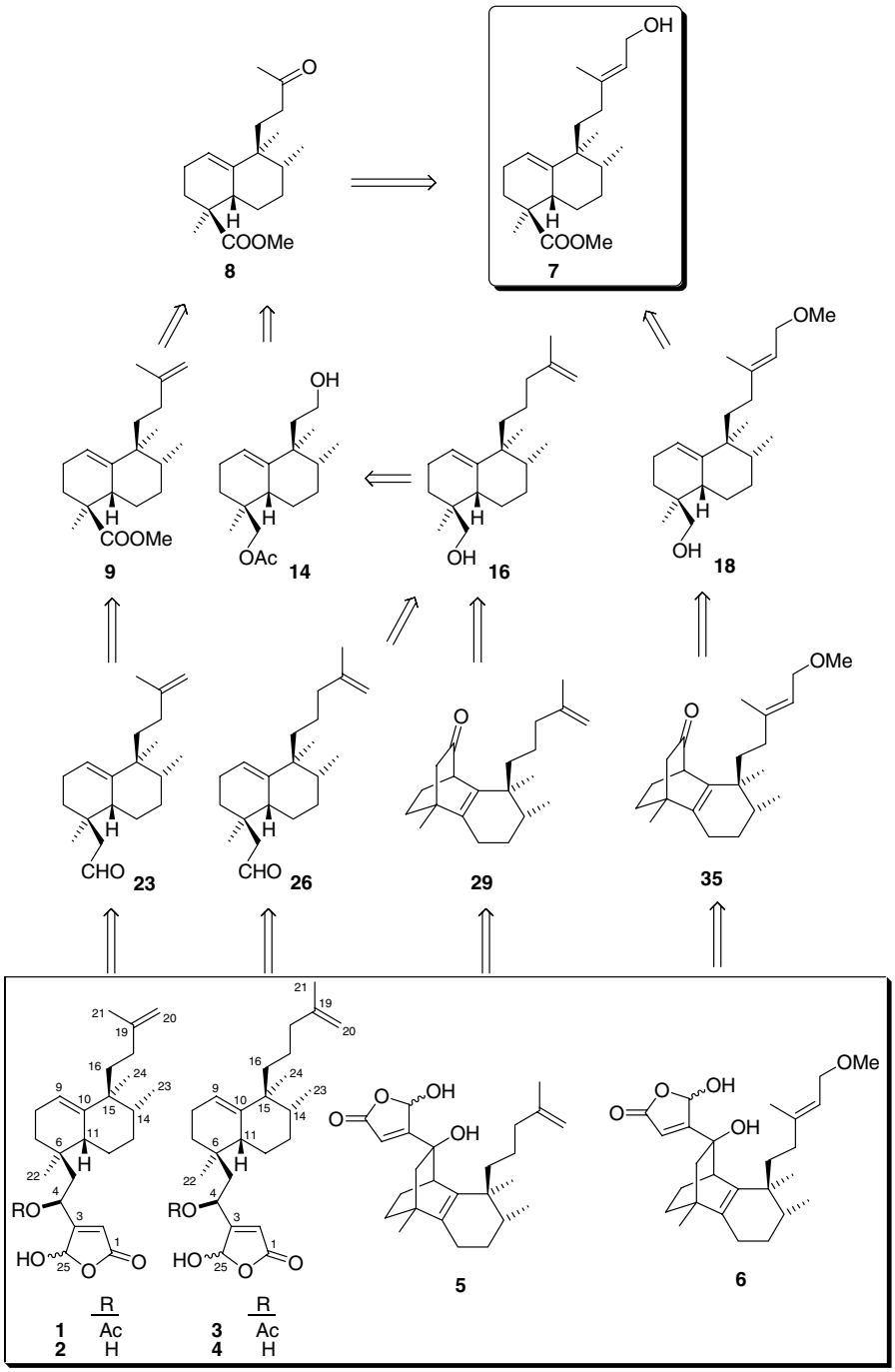
Therefore the synthesis of these compounds will be described in three parts:

1. Preparation of intermediates **9**, **14/16** and **18**.
2. Synthesis of aldehydes **23**, **26** and ketones **29**, **35**.
3. Synthesis of the γ-hydroxybutenolides **1**–**4** and **5**, **6**.

2.1. Preparation of intermediates 9, 14/16 and 18

Synthesis of **8** from *ent*-halimic acid methyl ester **7** in a 95% overall yield has been previously reported by us.[27] The synthesis of the intermediates **9** and **16**, that possess already the north chain of the final objective compounds **1/2**, **3/4** and **5**, was achieved from methylketone **8** (Scheme 2), by Wittig reaction with CH_3PPh_3Br in presence of NaHMDS,[28] to give **9** in an excellent yield.

Once obtained **9**, the synthesis of **16** was carried out as follows: reaction of **9** with *p*-TsOH gives chemoselective isomerization of the double bond in the side chain affording **10** in quantitative yield, which on reduction leads to hydroxyderivative **11**, that by acetylation gives the acetylderivative **12**. The chemoselective oxidation of the side chain double bond on **12** with *m*-CPBA, and subsequent oxidation with H_5IO_6, affords the tetranorderivative **13**. Reduction of **13** with $NaBH_4$ gives the hydroxyderivative **14**, that by tosylation gives the tosylderivative **15** in excellent yield. Treatment of the latter



Scheme 1.

with 2-methylallylmagnesium chloride affords **16**. The overall yield for the last two steps is higher than 87%.

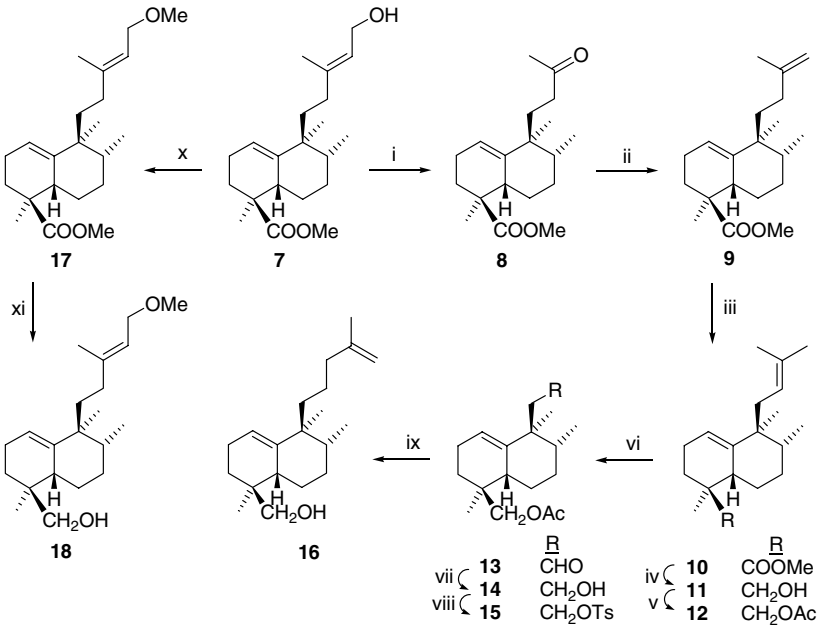
The synthesis of intermediate **18** (Scheme 2) is straightforward from **7**, by methylation of the hydroxy group on C-15 affording **17** and subsequent reduction of methoxycarbonyl group.

2.2. Synthesis of aldehydes 23, 26 and ketones 29, 35

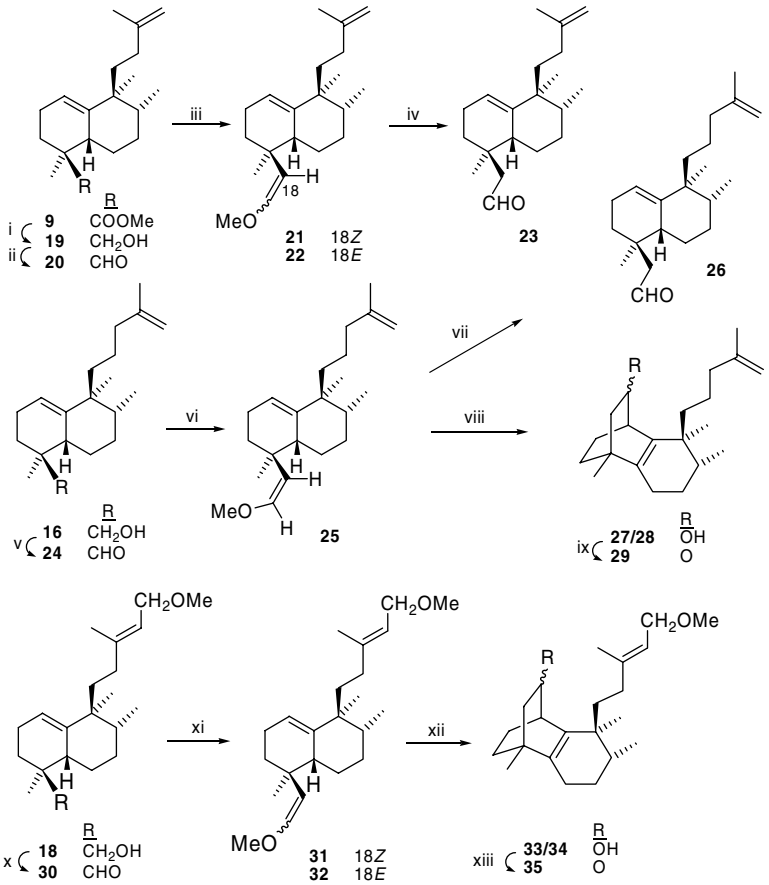
For the transformation of **9**, **16** and **18** into its carbonyl derivatives with one extra carbon **23**, **26**, **29** and **35**, the same synthetic strategy was used (Scheme 3).

Reaction of **9** with LAH (Scheme 3) and oxidation of the hydroxyderivative obtained **19** with TPAP[29] leads to aldehyde **20** in excellent yield. Oxidation of **16** and **18** with TPAP gave aldehydes **24** and **30** (Scheme 3), respectively, in excellent yields as well.

By reaction of **20**, **24** and **30** with $MeOCH_2PPh_3Cl$ in the presence of NaHMDS enolethers **21**/**22**, **25** and **31**/**32** are obtained, respectively. But in the case of **20** and **30** mixtures of enolethers **21***Z*/**22***E* (3:1) and **31***Z*/**32***E* (8:1) were obtained, respectively, being its configuration established by ^1H NMR. Surprisingly in the case of **24** only traces of the *E* isomer, **32**, were observed.



Scheme 2. Reagents and conditions: i—Ref. 27; ii—CH_3PPh_3Br, NaHMDS, −78 °C, 4 h (87%); iii—*p*-TsOH, Bencene, 60 °C, 2 h (99%); iv—LAH, Et_2O, 30 min (98%); v—Ac_2O, Pyridine, rt, overnight (97%); vi—(a) *m*-CPBA, CH_2Cl_2, 1 h (b) H_5IO_6, THF/H_2O, 30 min (98%, 2 steps); vii—$NaBH_4$, EtOH, rt, 30 min (87%); viii—TsCl, Pyridine, rt, overnight (95%); ix—2-methylallylmagnesium chloride, THF, 0 → rt, 2 h (92%); x—NaH, MeI, THF, rt, 2 h (92%); xi—LAH, Et_2O, 1 h (96%).



Scheme 3. Reagents and conditions: i—LAH, Et_2O, 30 min (98%); ii—TPAP, NMO, DCM, rt, 2 h (95%); iii—$MeOCH_2PPh_3Cl$, NaHMDS, THF, −78 °C, 1 h (92%, *Z*/*E*: 3:1); iv—*p*-TsOH, Me_2CO, H_2O (0.03M), rt, 3 h (91%); v—TPAP, NMO, DCM, rt, 1 h (96%); vi—$MeOCH_2PPh_3Cl$, NaHMDS, THF, −78 °C, 1 h (91%); vii—*p*-TsOH, Me_2CO, H_2O (0.03 M), rt, 3 h (96%); viii—*p*-TsOH, Me_2CO, H_2O (0.14 M), rt, overnight (**27**: 65%; **28**: 30%); ix—TPAP, NMO, DCM, rt, 30 min (95%); x—TPAP, NMO, DCM, rt, 40 min (95%); xi—$MeOCH_2PPh_3Cl$, NaHMDS, THF, −78 °C, 30 min (93%, *Z*/*E*: 8:1); xii—*p*-TsOH, Me_2CO, H_2O (0.14 M), rt, 1 h (**33**: 57%; **34**: 33%); xiii—TPAP, NMO, DCM, rt, 2 h (78%).

Synthesis of **23** and **26** needs a careful acid hydrolysis to avoid collateral reactions. The best conditions to do this are: to a 0.03 M solution of **21/22** or **25** in acetone/H_2O (45:1) add *p*-TsOH (0.3 mol/mol) for each case, respectively, avoiding concentrated acid media, in this manner **23** and **26** were obtained in 76 and 84% overall yields from **9** and **16**, respectively.

Reaction of enolethers **25** and **31/32** (Scheme 3) with *p*-TsOH 0.14 M (acetone/H_2O 45:1) affords the mixtures **27/28** and **33/34** which under oxidation with TPAP lead to ketones **29** and **35**, respectively. Cyclization products **27/28** and **33/34** appear because a Prins reaction takes place between the aldehyde generated 'in situ' and the annular olefin. Configuration on C-18 for **33** and **34** had been established before.[26]

2.3. Synthesis of the γ-hydroxybutenolides 1–4 and 5, 6

Last steps in the synthesis of compounds **1**–**4** and **5**, **6** are similar for the precedent four carbonyl compounds. It was done in two steps as indicated in Scheme 4. First of all, the four-carbon fragment was introduced by addition of the furyllithium and then we proceed with the furan oxidation following Faulkner's methodology.[30]

This part will be divided in two main chapters: first transformation of aldehydes **23** and **26** into γ-hydroxybutenolides **1**, **2** and **3**, **4** (Scheme 4), respectively, and second, transformation of ketones **29** and **35** into γ-hydroxybutenolides **5** and **6**. (Scheme 5).

2.3.1. Synthesis of the γ-hydroxybutenolides objectives 1, 2, 3 and 4. The synthesis of these γ-hydroxybutenolides is shown in the following scheme (Scheme 4).

By reaction of **23** and **26** with 3-furyllithium, generated 'in situ' by treatment of 3-bromofuran with *n*-BuLi,[31] hydroxyderivatives **36/37** and **39/41** were obtained, respectively (Scheme 4), which were separated by column chromatography. The configuration of the new stereocentre generated was established by Mosher's method.[32]

Oxidation of **36**, **37**, **39** and **41** (Scheme 4) with singlet oxygen at −78 °C in the presence of DIPEA (diisopropylethylamine)[30] leads to γ-hydroxybutenolides **2a**, **2b**, **4a** and **4b**, respectively, with very good yields in all the cases. The ^{1}H NMR spectra of all of them show the presence of a mixture 6:4 of epimers at C-25.

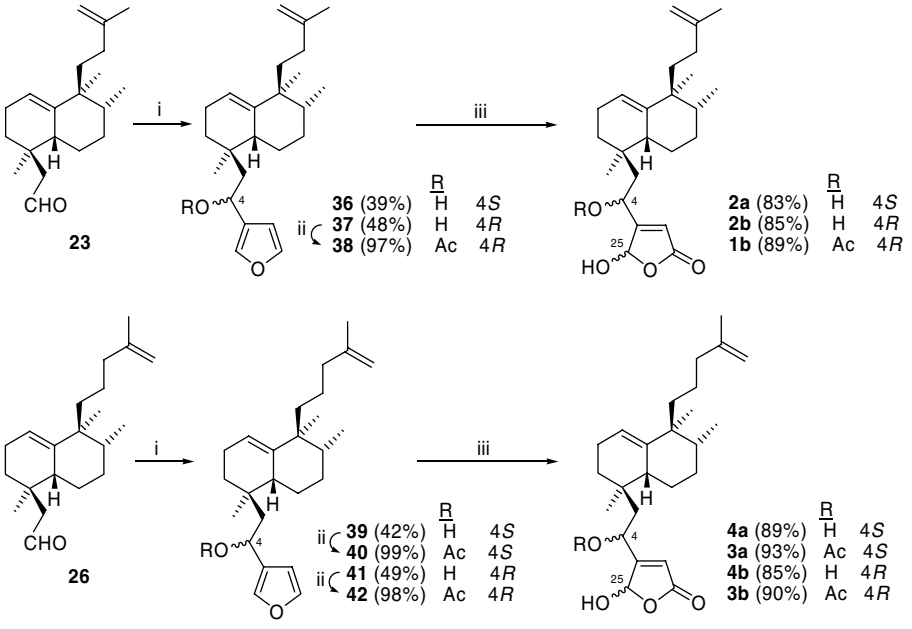
The structure of **4a** was corroborated by X-ray analysis (Fig. 2).[33] In this figure is shown besides **4a** X-ray figure, the dysidiolide enantiomer published by Gunasekera et al.[7] The similarity between these structures and the correspondence among the functional groups led us to suppose that the interaction of these with a biological substrate will be the same for both molecules and consequently must have similar biological activities.

The acetylation of **37**, **39** and **41** gave the acetylderivatives **38**, **40** and **42**, respectively, that by treatment with singlet oxygen (Scheme 4), affords the corresponding butenolides **1b**, **3a** and **3b**.

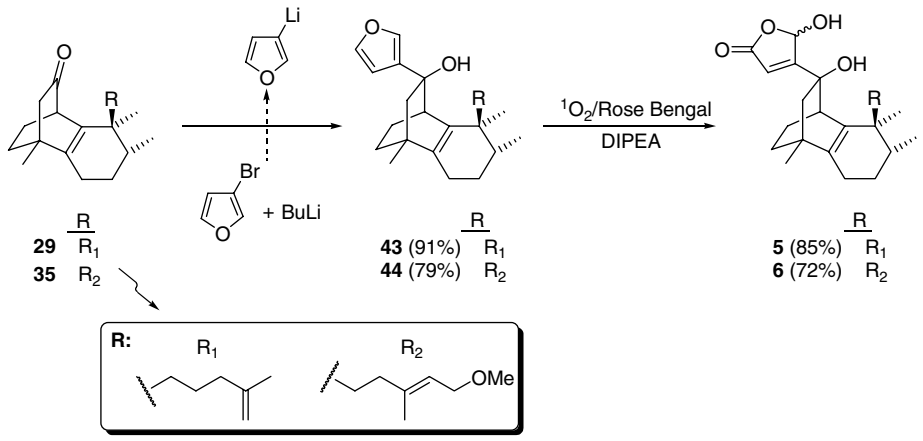
The structure for **3b** was corroborated by X-ray studies (Fig. 3).[34]

2.3.2. Transformation of ketones 29 and 35 into the γ-hydroxybutenolides 5 and 6. Addition of 3-furyllithium to **29** and **35** (Scheme 5) gives hydroxyderivatives **43** and **44**.

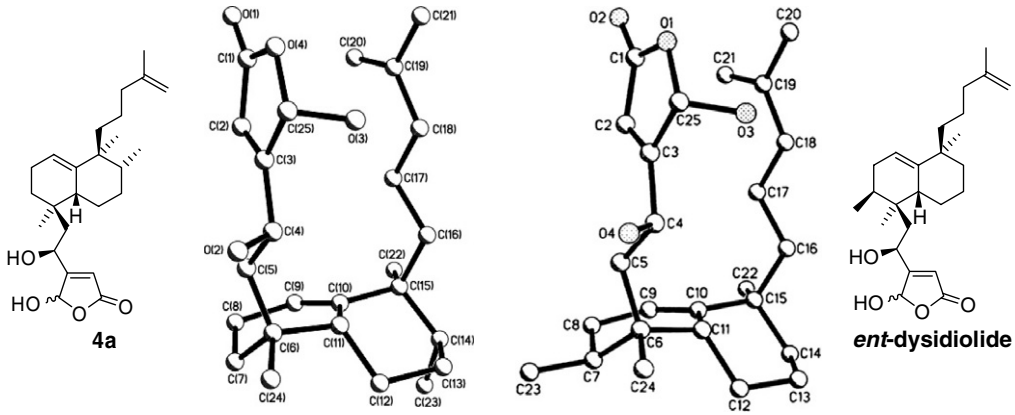
Oxidation with singlet oxygen of corresponding furilderivatives **43** and **44** led to the γ-hydroxybutenolides **5**[37] and **6**. Configuration on C-18 was established by



Scheme 4. Reagents and conditions: i—3-Bromofuran, *n*-BuLi, THF, −78 °C; ii—Ac_2O, Pyridine, rt; iii—$^1O_2$, DIPEA, Rose Bengal, THF, −78 °C.



Scheme 5.

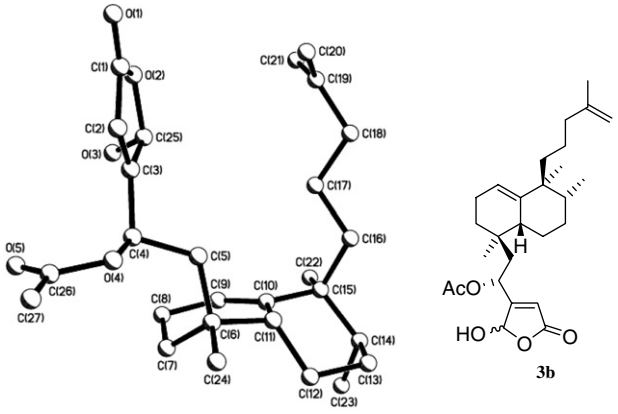


ORTP view of **4a** ORTP view of dysidiolide enantiomer[7]

Figure 2.

NMR experiments. In the ROESY experiment was observed a nOe between H-2 and H-7β fixing as 4*R* the new stereocentre. The remaining structurally important nOes are represented with arrows in Figure 4.

Addition of furyllithium to **35** must take place in the same way as in **29**, because **6** also possesses 4*R* configuration.



ORTP view of **3b**

Figure 3.

From hydroxyfurans **39** and **41** (Scheme 6) two new derivatives were obtained **45** and **46** in order to check its activities. Compound **45** was obtained by oxidation and isomerization of **45** afforded compound **46**.

In this manner we have obtained several analogues of dysidiolide that we proceed to study the antitumour activity.

3. Antitumour activity of dysidiolide analogues

The in vitro antitumour activity for these compounds was determined by measurement of their cytostatic and cytotoxic properties in human tumour cell lines by

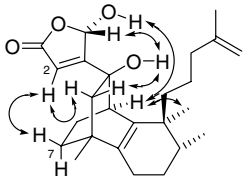
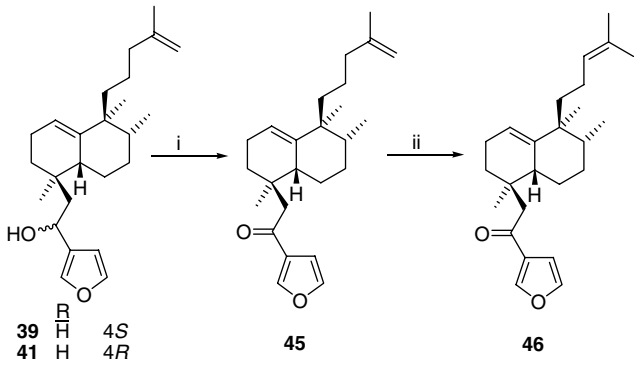


Figure 4.



Scheme 6. Reagents and conditions: i—TPAP, NMO, DCM, rt, 3 h (93%); ii—*p*-TsOH, Me_2CO, H_2O (0.03 M), 55 °C, 24 h (74%).

Table 1. Inhibition of proliferation of human tumour cell lines by structurally related compounds to dysidiolide

Compound	IC_{50} (10^{-6} M)			
	HeLa	A549	HT-29	HL-60
1b	6.7 ± 1.2	11.1 ± 3.6	4.8 ± 0.7	3.3 ± 0.6
2a	4.8 ± 0.7	4.5 ± 0.8	3.2 ± 0.1	3.2 ± 0.6
2b	5.4 ± 0.8	4.4 ± 0.6	3.6 ± 0.2	3.3 ± 0.3
3a	2.6 ± 0.5	4.5 ± 0.3	4.2 ± 0.5	3.0 ± 0.5
3b	3.5 ± 0.3	3.2 ± 0.4	2.9 ± 0.3	3.2 ± 0.3
4a	3.8 ± 0.5	3.2 ± 0.2	3.0 ± 0.4	3.0 ± 0.2
4b	2.6 ± 0.3	3.8 ± 0.5	2.3 ± 0.4	3.2 ± 0.3
5	3.1 ± 0.2	3.0 ± 0.4	2.9 ± 0.3	0.3 ± 0.1
6	26.5 ± 3.3	28.2 ± 1.9	18.7 ± 3.8	18.7 ± 1.7
36/37	30.2 ± 1.9	34.0 ± 3.4	30.0 ± 2.0	28.7 ± 2.3
39/41	59.4 ± 8.7	66.0 ± 8.9	63.1 ± 7.6	31.2 ± 3.2
45	>100	>100	>100	>100
46	54.5 ± 10.2	91.0 ± 12.3	82.3 ± 11.7	57.8 ± 7.3

Data are shown as the mean values ± SE of three independent determinations.

XTT assay (Table 1). The cell lines used were HeLa (human epitheloid cervix carcinoma), A549 (human lung carcinoma), HT-29 (human colon carcinoma), and HL-60 (human myeloid leukaemia).

Cells were incubated in DMEM (HeLa, A549, HT-29) or RPMI1640 (HL-60) culture medium containing 10% heat-inactivated foetal bovine serum in the absence and in the presence of the indicated compounds at a concentration range of 10^{-4} to 10^{-8} M in a 96-well plate, and following 72 h of incubation at 37 °C in a humidified atmosphere of air/CO_2 (19:1) the XTT assay was performed. Measurements were done in triplicate, and the IC_{50} value, defined as the drug concentration required to cause 50% inhibition in the cellular proliferation with respect to the untreated controls, was determined for each compound.

The proliferation inhibition data showed a significant antitumour activity of the compounds **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5**, inhibiting proliferation of distinct cancer cell types with an IC_{50} in the low micromolar range (Table 1).

By comparison of the structure of distinct dysidiolide analogues with their corresponding cytotoxic activities (Table 1), we could analyze the portions of the dysidiolide molecular structure required for its antitumour activity. We found that the presence of the γ-hydroxybutenolide moiety is essential for this activity, as its replacement for a furan ring (compounds **36**, **37**, **39**, **41**, **45**, **46**) led to a dramatic increase in the IC_{50}. In addition, a homoisoprenyl group at C-15 seems to render slightly more potent antitumour compounds than a isoprenyl group in the same position (cf. IC_{50} values between **4a/4b** and **2a/2b**). A significant modification at the isoprenyl group, such as that carried out in compound **6**, leads to a drastic reduction in the antitumour activity of the compound (cf. IC_{50} values between compounds **5** and **6**). The presence of either a hydroxy or an acetyl group between the γ-hydroxybutenolide moiety and the bicyclic framework does not affect significantly the antitumour activity of compounds **3a/3b** and **4a/4b** (cf. IC_{50} values of **3a/3b** and **4a/4b**), the hydroxyl analogue **2a** is slightly more active than the acetyl-derivative **1b**.

The configuration at C-4 seems not to affect the biological activity, see **2a/2b**, **3a/3b** and **4a/4b**, Table 1.

Interestingly, lactone compound **5** with a tricyclic framework shows the highest activity against leukaemic HL-60 cells (Table 1). This could be related to the fact that HL-60 cells divide more rapidly than the solid tumour cells HeLa, A549 and HT-29, and dysidiolide has been reported to inhibit cdc25A causing cell cycle arrest.[7]

4. Conclusions

Nine sesterterpenolides analogues of dysidiolide have been synthesised and their in vitro antitumour activity has been studied. These results indicate that these compounds are slightly more potent and act in same range of concentrations as dysidiolide.

5. Experimental

5.1. General methods

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200/400 and 50/100 MHz, respectively. The 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. Chemical shifts are reported in δ (ppm) and coupling constants (*J*) are given in Hz. Diethyl ether, THF and benzene were distilled from sodium, and pyridine and dichloromethane were distilled under argon from CaH_2.

5.1.1. Reaction of 8 with CH_3PPh_3/NaHMDS: methyl 15-nor-*ent*-halima-1(10),13-dien-18-oate (9). To a suspension of CH_3PPh_3Br (2.86 g, 8.00 mmol) in THF (15 mL) at −20 °C under Ar atmosphere, 1.0 M NaHMDS in THF (8.0 mL, 8.00 mmol) was added dropwise

and the solution was stirred for 30 min at room temperature. The reaction mixture was recooled to −78 °C and a solution of **8** (814 mg, 2.66 mmol) in THF (8 mL) was added dropwise and the mixture was stirred for 4 h at room temperature. It was quenched with aqueous NH_4Cl at −78 °C and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. The residue obtained after solvent removal was purified by column chromatography (Hex/EtOAc 95:5) to afford **9** (704 mg, 87%). $[\alpha]_D^{22}$ + 59.8 (*c* 0.98, $CHCl_3$); IR (film, cm^{-1}) 3090, 2936, 1732, 1451, 1379, 1258, 1196, 1163, 1113, 1022, 883, 804; ^1H NMR (200 MHz, $CDCl_3$) δ 5.33 (1H, t, J = 3.4 Hz, H-1), 4.68 (2H, br s, H-14), 3.64 (3H, s, –COO*Me*), 2.74–2.62 (1H, m, H-5), 1.73 (3H, s, Me-16), 2.16–1.19 (13H, m), 1.11 (3H, s, Me-19), 0.91 (3H, s, Me-20), 0.80 (3H, d, J = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.9 (C-1), 23.0 (C-2), 30.8 (C-3), 45.1 (C-4), 38.6 (C-5), 23.1 (C-6), 28.6 (C-7), 38.7 (C-8), 43.0 (C-9), 141.5 (C-10), 37.8 (C-11), 32.4 (C-12), 147.5 (C-13), 109.3 (C-14), 22.6 (C-16), 15.8 (C-17), 178.8 (C-18), 20.3 (C-19), 22.6 (C-20), 51.9 (–COO*Me*); EIMS [*m*/*z* (%)] 304 (M^+, 7), 245 (36), 235 (93), 175 (100), 105 (24), 91 (13), 69 (12); HREIMS calcd for $C_{20}H_{32}O_2$ (M^+) 304.2402, found (M^+) 304.24111.

5.1.2. Isomerization of 9 with *p*-TsOH: methyl 15-nor-*ent*-halima-1(10),12-dien-18-oate (10). To a solution of **9** (1.89 g, 6.22 mmol) in benzene (63 mL), *p*-TsOH (291 mg, 1.69 mmol) was added. The reaction mixture was stirred at 60 °C for 2 h. It was cooled and diluted with Et_2O. It was washed with 6% aqueous $NaHCO_3$ and brine. Evaporation of the solvent yielded **10** (1.88 g, 99%). The residue obtained after solvent removal was purified by column chromatography (Hex/AcOEt 85:15) to afford **10** (1.88 g, 99%). $[\alpha]_D^{22}$ − 15.4 (*c* 1.7, $CHCl_3$); IR (film, cm^{-1}) 1732, 1452, 1379, 1250, 1196, 1163, 1111; ^1H NMR (200 MHz, $CDCl_3$) δ 5.32 (1H, s, H-1), 5.03–4.96 (1H, m, H-12), 3.65 (3H, s, –COO*Me*), 2.79–2.73 (1H, m, H-5), 2.15–1.96 (4H, m), 1.83–1.16 (7H, m), 1.68 (3H, s, Me-16), 1.60 (3H, s, Me-14), 1.11 (3H, s, Me-19), 0.86 (3H, s, Me-20), 0.79 (3H, d, J = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 121.8 (C-1), 22.9 (C-2), 31.2 (C-3), 45.2 (C-4), 38.1 (C-5), 23.0 (C-6), 28.7 (C-7), 38.7 (C-8), 43.8 (C-9), 141.7 (C-10), 38.0 (C-11), 119.5 (C-12), 132.1 (C-13), 18.3 (C-14), 19.6 (C-16), 15.8 (C-17), 178.9 (C-18), 16.3 (C-19), 26.3 (C-20), 51.9 (–COO*Me*); EIMS [*m*/*z* (%)] 304 (M^+, 10), 235 (85), 175 (100), 105 (20), 69 (15); HREIMS calcd for $C_{20}H_{32}O_2$ $(M)^+$ 304.2402, found (M^+) 304.2412.

5.1.3. Reduction of 10 with LAH: 15-nor-*ent*-halima-1(10),12-dien-18-ol (11). To an ice cooled solution of **10** (664 mg, 2.18 mmol) in Et_2O (14 mL), LAH (92 mg, 2.42 mmol) was added. The reaction mixture was stirred at room temperature for 30 min. It was cooled to 0 °C and the excess of LAH was decomposed by dropwise addition of aqueous Et_2O. After filtration, the solvent was evaporated to give a residue which was purified by silica gel column chromatography (Hex/EtOAc 9:1) to yield **11** (590 mg, 98%). $[\alpha]_D^{22}$ − 15.4 (*c* 1.7, $CHCl_3$), IR (film, cm^{-1}) 1732, 1452, 1379, 1250, 1196, 1163, 1111; ^1H RMN (200 MHz, $CDCl_3$) δ 5.32 (1H, s, H-1), 5.03-4.96 (1H, m, H-12), 3.65 (3H, s, –COO*Me*), 2.79–2.73 (1H, m, H-5), 2.15-1.96 (4H, m), 1.83–1.16 (7H, m), 1.68 (3H, s, Me-16), 1.60 (3H, s, Me-14), 1.11 (3H, s, Me-19), 0.86 (3H, s, Me-20), 0.79 (3H, d, J = 7.0 Hz, Me-17); ^{13}C RMN (50 MHz, $CDCl_3$) δ 121.8 (C-1), 22.9 (C-2), 31.2 (C-3), 45.2 (C-4), 38.1 (C-5), 23.0 (C-6), 28.7 (C-7), 38.7 (C-8), 43.8 (C-9), 141.7 (C-10), 38.0 (C-11), 119.5 (C-12), 132.1 (C-13), 18.3 (C-14), 19.6 (C-16), 15.8 (C-17), 178.9 (C-18), 16.3 (C-19), 26.3 (C-20), 51.9 (–COO*Me*); IEMS [*m*/*z* (%)] 304 (M^+, 10), 235 (85), 175 (100), 105 (20), 69 (15) HRIEMS calcd $C_{20}H_{32}O_2$ $(M)^+$ 304.2402, found 304.2412.

5.1.4. Reaction of acetylation of 11: 18-acetate de 15-nor-*ent*-halima-1(10),12-dienyl (12). To a solution of **11** (585 mg, 2.12 mmol) in dry pyridine (3 mL), Ac_2O (2 mL) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice-water and extracted with Et_2O. The organic layer was washed successively with 2 M aqueous HCl, 6% aqueous $NaHCO_3$ and brine. Evaporation of the dried extract gave a residue which was purified by column chromatography (Hex/EtOAc 97:3) to afford **12** (655 mg, 97%). $[\alpha]_D^{22}$ + 15.8 (*c* 1.03, $CHCl_3$); IR (film, cm^{-1}) 3052, 2932, 1744, 1451, 1371, 1240, 1036; ^1H NMR (200 MHz, $CDCl_3$) δ 5.31 (1H, t, J = 3.6 Hz, H-1), 4.92 (1H, t, J = 7.2 Hz, H-12), 3.88 (1H, d, J = 10.7 Hz, H_A-18), 3.75 (1H, d, J = 10.7 Hz, H_B-18), 2.47 (1H, dd, J = 14.8 and 6.4 Hz, H-5), 2.03 (3H, s, –OOC*Me*), 1.67 and 1.59 (3H, s ea, Me-14 and Me-16), 2.18–0.92 (11H, m), 0.87 (6H, s, Me-19 and Me-20), 0.80 (3H, d, J = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.7 (C-1), 22.7 (C-2), 29.4 (C-3), 35.2 (C-4), 38.5 (C-5), 23.5 (C-6), 28.9 (C-7), 38.7 (C-8), 44.0 (C-9), 141.7 (C-10), 37.6 (C-11), 121.5 (C-12), 132.2 (C-13), 26.2 (C-14), 18.3 (C-16), 15.8 (C-17), 70.8 (C-18), 21.2 (C-19), 23.1 (C-20), 171.6 (–O*OC*Me), 21.3 (–OOC*Me*); EMIE [*m*/*z* (%)] 318 (M^+, 3), 235 (31), 189 (100), 105 (25), 69 (16); HREIMS calcd for $C_{21}H_{34}O$ (M^+) 318.2559, found (M^+) 318.2566.

5.1.5. Epoxydation of 12 with *m*-CPBA and oxidation with H_5IO_6: 18-acetoxy-13,14,15,16-tetranor-*ent*-halim-1(10)-en-12-al (13). A solution of *m*-CPBA (1.02 g, 5.93 mmol) in dry CH_2Cl_2 (25 mL) was added to an ice-cooled solution of **12** (1.71 g, 5.38 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 1 h. It was diluted with water and extracted with Et_2O. The organic layer was washed successively with 10% aqueous Na_2SO_3 solution, 6% aqueous $NaHCO_3$ solution and brine. To a solution of the residue, obtained by evaporation of the dried extract, in THF (22 mL) was added a suspension of H_5IO_6 (1.81 g, 7.94 mmol) in THF/H_2O (11 mL/4 mL). After 30 min water was added and the reaction mixture extracted with Et_2O. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution and brine. Evaporation of the dried solution gave a residue, which was chromatographed on silica gel (Hex/EtOAc 95:5) to afford **13** (719 mg, 77%). $[\alpha]_D^{22}$ + 6.3 (*c* 1.02, $CHCl_3$); IR (film, cm^{-1}) 3050, 2932, 2731, 1744, 1717, 1456, 1373, 1242, 1038; ^1H NMR (200 MHz, $CDCl_3$) δ 9.58 (1H, dd,

J = 3.8 and 1.2 Hz, H-12), 5.52 (1H, t, J = 3.6 Hz, H-1), 3.87 (1H, d, J = 10.6 Hz, H_A-18), 3.79 (1H, d, J = 10.6 Hz, H_B-18), 2.89 (1H, dd, J = 14.6 and 1.2 Hz, H_A-11), 2.17 (1H, dd, J = 14.6 and 3.8 Hz, H_B-11), 2.06 (3H, s, –OOC*Me*), 2.20–1.16 (10H, m), 1.13 (3H, s, Me-20), 0.88 (3H, s, Me-19), 0.83 (3H, d, J = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 121.6 (C-1), 22.5 (C-2), 29.5 (C-3), 35.4 (C-4), 38.4 (C-5), 23.0 (C-6), 29.0 (C-7), 39.1 (C-8), 42.5 (C-9), 139.6 (C-10), 51.8 (C-11), 204.0 (C-12), 14.9 (C-17), 70.7 (C-18), 20.6 (C-19), 24.1 (C-20), 171.5 (–O*OC*Me), 21.2 (–OOC*Me*); EMIE [*m*/*z* (%)] 292 (M^+, 1), 274 (10), 248 (47), 219 (100), 175 (77), 145 (28), 105 (44), 91 (33), 77 (37); HREIMS calcd for $C_{18}H_{28}O_3$ (M^+) 292.2038, found (M^+) 292 2042.

5.1.6. Reduction of 13 with $NaBH_4$: 18-acetoxy-13,14,15, 16-tetranor-*ent*-halim-1(10)-en-12-ol (14). To an ice-cooled solution of mixture **13** (703 mg, 2.41 mmol) in EtOH (24 mL), $NaBH_4$ (138 mg, 3.61 mmol) was added. After being stirred at room temperature for 30 min, 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 a residue, which was chromatographed on silica gel (Hex/EtOAc 95:5) to afford **14** (678 mg, 96%). $[\alpha]_D^{22}$ + 56.6 (*c* 1.07, $CHCl_3$); IR (film, cm^{-1}) 3426, 3050, 2934, 1740, 1456, 1373, 1242, 1044; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.37 (1H, t, J = 3.2 Hz, H-1), 3.88 (1H, d, J = 10.6 Hz, H_A-18), 3.82 (1H, d, J = 10.6 Hz, H_B-18), 3.56 (1H, dt, J = 9.8 and 5.8 Hz, H_A-12), 3.44 (1H, dt, J = 9.8 and 5.8 Hz, H_B-12), 2.23 (1H, dt, J = 9.6 and 5.8 Hz, H_A-11), 2.21 (1H, dt, J = 9.6 and 5.8 Hz, H_B-11), 2.05 (3H, s, –OOC*Me*), 2.13–1.85 (4H, m), 1.65–1.16 (6H, m), 0.95 (3H, s, Me-20), 0.87 (3H, s, Me-19), 0.77 (3H, d, J = 6.8 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.0 (C-1), 22.5 (C-2), 29.0 (C-3), 35.3 (C-4), 38.2 (C-5), 23.4 (C-6), 29.0 (C-7), 39.3 (C-8), 42.2 (C-9), 141.5 (C-10), 41.6 (C-11), 59.8 (C-12), 15.3 (C-17), 70.8 (C-18), 21.1 (C-19), 22.9 (C-20), 171.8 (–O*OC*Me), 21.1 (–OOC*Me*); EMIE [*m*/*z* (%)] 294 (M^+, 3), 281 (4), 249 (14), 221 (56), 189 (100), 161 (23), 105 (31), 77 (22); HREIMS calcd for $C_{18}H_{30}O_3$ (M^+) 294.2195, found (M^+) 294.2187.

5.1.7. Reaction of 14 with TsCl: 18-acetate of 12-*p*-toluenesulfonyloxi-13,14,15,16-tetranor-*ent*-halimen-1 (10)-yl (15). To an ice cooled solution of **14** (562 mg, 1.91 mmol) in pyridine (20 mL) was added TsCl (1.10 g, 5.77 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was poured into ice-water and extracted with Et_2O. The extracts were washed successively with 2 M aqueous HCl solution, 6% aqueous $NaHCO_3$ solutionand water, and dried over Na_2SO_4. Filtration, concentration and silica gel column chromatography (Hex/EtOAc 85:15) gave **15** (812 mg, 95%). $[\alpha]_D^{22}$ + 7.4 (*c* 1.12, $CHCl_3$); IR (film, cm^{-1}) 3050, 2936, 1738, 1456, 1362, 1242, 1177, 1098, 1036, 957, 816; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.73 (2H, d, J = 8.2 Hz, H-2′ and H-6′), 7.30 (2H, d, J = 8.2 Hz, H-3′ and H-5′), 5.25 (1H, t, J = 3.6 Hz, H-1), 3.87 (1H, dt, J = 10.0 and 6.6 Hz, H_A-12), 3.80 (1H, d, J = 11.0 Hz, H_A-18), 3.79 (1H, dt, J = 10.0 and 6.6 Hz, H_B-12), 3.66 (1H, d, J = 11.0 Hz, H_B-18), 2.39 (3H, s, Ph-*Me*), 2.27 (1H, dt, J = 9.2 and 6.6 Hz, H_A-11), 2.24 (1H, dt, J = 9.2 and 6.6 Hz, H_B-11), 2.03 (3H, s, –OOC*Me*), 2.14–1.67 (4H, m), 1.60–1.05 (6H, m), 0.83 (3H, s, Me-19), 0.79 (3H, s, Me-20), 0.72 (3H, d, J = 6.8 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 121.2 (C-1), 22.5 (C-2), 29.3 (C-3), 35.3 (C-4), 38.2 (C-5), 22.9 (C-6), 28.8 (C-7), 39.0 (C-8), 42.1 (C-9), 139.9 (C-10), 37.5 (C-11), 68.6 (C-12), 15.2 (C-17), 70.6 (C-18), 20.5 (C-19), 22.9 (C-20), 171.5 (–O*OC*Me), 21.1 (–OOC*Me*), 133.5 (C-1′), 128.1 (C-2′ and C-6′), 130.0 (C-3′ and C-5′), 144.8 (C-4′), 21.8 (Ph-*Me*); EMIE [*m*/*z* (%)] 448 (M^+, 1), 388 (16), 221 (22), 189 (100), 153 (30), 77 (52); HREIMS calcd for $C_{25}H_{36}O_5S$ (M^+) 448.2283, found (M^+) 448.2276.

5.1.8. Reaction of 15 with CH_2 =C(CH_3)CH_2 MgCl: 16(13 → 14)abeo-*ent*-halima-1(10),14-dien-18-ol (16). A solution of 0.5 M in THF 2-methyl-2-propenyl magnesium chloride (100 mL, 50.00 mmol) was added to an ice cooled solution of **21** (753 mg, 1.68 mmol) in THF (3 mL) under Ar. The mixture was allowed to warm to room temperature and stirred for 4 h. Then, it was cooled, quenched with a saturated NH_4Cl aqueous solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was chromatographed on silica gel (Hex/EtOAc 95:5) to yield **16** (450 mg, 92%). $[\alpha]_D^{22}$ + 45.4 (*c* 0.95, $CHCl_3$); IR (film, cm^{-1}) 3364, 3073, 2934, 1647, 1456, 1379, 1044, 885; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30 (1H, t, J = 3.6 Hz, H-1), 4.65 (1H, br s, H_A-15), 4,63 (1H, br s, H_B-15), 3.46 (1H, d, J = 10.6 Hz, H_A-18), 3.23 (1H, d, J = 10.6 Hz, H_B-18), 2.31 (1H, br s, –OH), 2.80–1.74 (7H, m), 1.67 (3H, s, Me-16), 2.61–0.97 (9H, m), 0.87 (3H, s, Me-19), 0.83 (3H, s, Me-20), 0.78 (3H, d, J = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.8 (C-1), 22.8 (C-2), 29.2 (C-3), 36.7 (C-4), 38.1 (C-5), 23.5 (C-6), 28.7 (C-7), 39.1 (C-8), 43.2 (C-9), 142.0 (C-10), 39.0 (C-11), 22.3 (C-12), 38.8 (C-13), 146.5 (C-14), 109.9 (C-15), 22.8 (C-16), 15.8 (C-17), 69.8 (C-18), 20.8 (C-19), 22.6 (C-20); EMIE [*m*/*z* (%)] 290 (M^+, 8), 259 (73), 207 (100), 177 (41), 149 (34), 105 (41); HREIMS calcd for $C_{20}H_{34}O$ (M^+) 290.2610, found (M^+) 290.2603.

5.1.9. Protection of 7 with MeI: methyl 15-methoxy-*ent*-halima-1(10),13*E*-dien-18-oate (17). To a solution of *ent*-halimic methyl ester **7** (238 mg, 0.71 mmol) in THF (12 mL) was added NaH 60% (288 mg, 7.20 mmol) and after few minutes, MeI (0.44 mL, 7.07 mmol) was added under argon atmosphere. The reaction mixture was stirred for 2 h, quenched with ice and extracted with Et_2O. The organic layer was washed successively with 2 M aqueous HCl and brine, and dried over Na_2SO_4. Filtration, concentration and silica gel column cromatography (Hex/EtOAc 9:1) afforded **17** (228 mg, 92%). $[\alpha]_D^{22}$ + 54.6 (*c* 1.15, $CHCl_3$); IR (film, cm^{-1}) 3073, 2947, 1732, 1462, 1379, 1111; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.38–5.23 (2H, m, H-1 and H-14), 3.87 (2H, d, J = 7.0 Hz, H-15), 3.60 (3H, s, –COO*Me*), 3.28 (3H,

s, –O*Me*), 2.70–2.54 (1H, m, H-5), 1.64 (3H, s, Me-16), 2.09–1.12 (13H, m), 1.07 (3H, s, Me-19), 0.87 (3H, s, Me-20), 0.76 (3H, d, $J = 7.0$ Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.6 (C-1), 22.8 (C-2), 30.7 (C-3), 44.9 (C-4), 38.4 (C-5), 22.9 (C-6), 28.4 (C-7), 38.4 (C-8), 42.8 (C-9), 141.6 (C-10), 37.8 (C-11), 34.0 (C-12), 141.3 (C-13), 120.2 (C-14), 69.1 (C-15), 16.6 (C-16), 15.5 (C-17), 178.3 (C-18), 19.8 (C-19), 22.4 (C-20), 57.7 (–O*Me*), 51.6 (–COO*Me*).

5.1.10. Reduction of 17 with LAH: 15-methoxy-*ent*-halima-1(10),13 *E*-dien-18-ol (18). Reduction of **17** (212 mg, 0.61 mmol) (as described before for compound **11**) yields after column chromatography over silica gel (Hex/EtOAc 85:15) compound **18** (187 mg, 96%). $[\alpha]_D^{22}$ + 64.6 (*c* 1.13, $CHCl_3$); IR (film, cm^{-1}) 3451, 3073, 2930, 1667, 1464, 1379, 1105; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.34–5.20 (2H, m, H-1 and H-14), 3.85 (2H, d, $J = 7.0$ Hz, H-15), 3.41 (1H, d, $J = 10.5$ Hz, H_A-18). 3.26 (3H, s, –O*Me*). 3.19 (1H, d, $J = 10.5$ Hz, H_B-18), 1.60 (3H, s, Me-16), 2.21–1.09 (14H, m), 0.84 (3H, s, Me-19), 0.79 (3H, s, Me-20), 0.76 (3H, d, $J = 7.0$ Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.0 (C-1), 22.6 (C-2), 28.9 (C-3), 36.4 (C-4), 37.8 (C-5), 23.2 (C-6), 28.6 (C-7), 39.0 (C-8), 43.0 (C-9), 141.5 (C-10), 37.5 (C-11), 34.3 (C-12), 141.5 (C-13), 120.2 (C-14), 69.0 (C-15), 16.5 (C-16), 15.5 (C-17), 69.4 (C-18), 20.5 (C-19), 22.3 (C-20), 57.6 (–O*Me*).

5.1.11. Reduction of 9 with LAH: 15-nor-*ent*-halima-1(10),13-dien-18-ol (19). Reduction of **9** (664 mg, 2.18 mmol) (as described before for compound **11**) yields after column chromatography over silica gel (Hex/EtOAc 9:1) compound **19** (590 mg, 98%). $[\alpha]_D^{22}$ + 63.3 (*c* 0.98, $CHCl_3$); IR (film, cm^{-1}) 3372, 2930, 1647, 1456, 1379, 1045, 883; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.33 (1H, t, $J = 3.4$ Hz, H-1), 4.64 (2H, br s, H-14), 3.49 (1H, d, $J = 10.8$ Hz, H_A-18), 3.26 (1H, d, $J = 10.8$ Hz, H_B-18), 1.71 (3H, s, Me-16), 2.15–1.08 (14H, m), 0.90 (3H, s, Me-19), 0.86 (3H, s, Me-20), 0.81 (3H, d, $J = 7.0$ Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.2 (C-1), 22.8 (C-2), 29.2 (C-3), 36.6 (C-4), 38.1 (C-5), 23.6 (C-6), 28.5 (C-7), 39.3 (C-8), 43.2 (C-9), 141.7 (C-10), 37.6 (C-11), 32.7 (C-12), 147.5 (C-13), 109.4 (C-14), 22.9 (C-16), 15.8 (C-17), 69.7 (C-18), 21.0 (C-19), 22.4 (C-20); EIMS [*m*/*z* (%)] 276 (M^+, 3), 245 (100), 207 (31), 177 (46), 149 (23), 119 (17), 95 (19), 69 (17); HREIMS calcd for $C_{19}H_{32}O$ (M^+) 276.2453, found (M^+) 276.2446.

5.1.12. Oxidation of 19 with TPAP: 15-nor-*ent*-halima-1(10),13-dien-18-al (20). To a mixture of **19** (547 mg, 1.98 mmol), *N*-methylmorpholine-*N*-oxide (NMO) (804 mg, 5.94 mmol) and molecular sieves (998 mg, 500 mg/mmol) in anhydrous CH_2Cl_2(20 mL) under Ar and at room temperature, TPAP (25 mg, 0.07 mmol) was added. The reaction mixture was stirred for 2 h and then filtered on silica gel and Celite (DCM and EtOAc). Evaporation of the solvent followed by chromatography on silica gel (Hex/EtOAc 9:1) yielded **20** (515 mg, 95%). $[\alpha]_D^{22}$ + 73.8 (*c* 0.90, $CHCl_3$); IR (film, cm^{-1}) 3073, 2930, 2693, 1726, 1649, 1451, 1379, 883; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.41 (1H, s, H-18), 5.33 (1H, t, $J = 3.4$ Hz, H-1), 4.66 (2H, br s, H-14), 2.52-2.31 (1H, m, H-5), 1.71 (3H, s, Me-16), 2.18-1.19 (13H, m), 0.95 (3H, s, Me-19), 0.90 (3H, s, Me-20), 0.80 (3H, d, $J = 7.0$ Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.5 (C-1), 22.5 (C-2), 28.7 (C-3), 48.1 (C-4), 36.2 (C-5), 23.2 (C-6), 27.8 (C-7), 38.9 (C-8), 43.2 (C-9), 141.2 (C-10), 37.6 (C-11), 32.6 (C-12), 147.3 (C-13), 109.4 (C-14), 23.0 (C-16), 15.8 (C-17), 206.6 (C-18), 17.6 (C-19), 22.5 (C-20); EIMS [*m*/*z* (%)] 245 (M^+−CHO, 16), 221 (27), 175 (36), 149 (28), 69 (100).

5.1.13. Reaction of 20 with $MeOCH_3$ PPh_3/NaHMDS: 18-methoxy-18a-homo-15-nor-*ent*-halima-1(10),13,18a(18)*Z*-triene (21) and 18-methoxy-18a-homo-15-nor-*ent*-halima-1(10),13,18a(18)*E*-triene (22). To a suspension of $MeOCH_2PPh_3Cl$ (1.78 g, 5.19 mmol) in THF (10 mL) at −78 °C under Ar atmosphere, 1.0 M NaHMDS in THF (5.1 mL, 5.10 mmol) was added dropwise and the solution was stirred for 30 min. A solution of the aldehyde **20** (474 mg, 1.73 mmol) in THF (7 mL) was added dropwise and the mixture was stirred for 1 h. It was quenched with aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. The residue obtained after solvent removal was purified by column chromatography (Hex/EtOAc 97:3) to afford the mixture **21/22** (480 mg, 92%), (*Z*/*E*: 3:1). *Compound* **21**: $[\alpha]_D^{22}$ + 57.4 (*c* 0.68, $CHCl_3$); IR (film, cm^{-1}) 3073, 2934, 1653, 1458, 1377, 1105, 883; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.68 (1H, d, $J = 7.0$ Hz, H-18) 5.33 (1H, t, $J = 3.4$ Hz, H-1), 4.65 (2H, br s, H-14), 4.14 (1H, d, $J = 7.0$ Hz, H-18a), 3.51 (3H, s, –O*Me*), 1.72 (3H, s, Me-16), 2.15–1.12 (14H, m), 1.07 (3H, s, Me-19), 0.90 (3H, s, Me-20), 0.81 (3H, d, $J = 7.0$ Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.5 (C-1), 23.5 (C-2), 31.4 (C-3), 36.4 (C-4), 43.3 (C-5), 23.6 (C-6), 29.3 (C-7), 39.4 (C-8), 43.1 (C-9), 142.0 (C-10), 37.7 (C-11), 32.6 (C-12), 147.7 (C-13), 109.1 (C-14), 23.0 (C-16), 15.9 (C-17), 116.5 (C-18a), 145.6 (C-18), 23.2 (C-19), 22.4 (C-20), 59.8 (–O*Me*); EIMS [*m*/*z* (%)] 302 (M^+, 5), 233 (13), 206 (10), 161 (8), 98 (100), 83 (11); HREIMS calcd for $C_{21}H_{34}O$ (M^+) 302.2610, found (M^+) 302.2601. *Compound* **22**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.23 (1H, d, $J = 14.2$ Hz, H-18) 5.35 (1H, t, $J = 3.4$ Hz, H-1), 4.82 (1H, d, $J = 14.2$ Hz, H-18a), 4.65 (2H, br s, H-14), 3.51 (3H, s, –O*Me*), 1.72 (3H, s, Me-16), 2.15–1.12 (14H, m), 0.92 (3H, s, Me-19), 0.90 (3H, s, Me-20), 0.81 (3H, d, $J = 7.0$ Hz, Me-17); EIMS [*m*/*z* (%)] 302 (M^+, 5), 233 (13), 206 (10), 161 (8), 98 (100), 83 (11); HREIMS calcd for $C_{21}H_{34}O$ (M^+) 302.2610, found (M^+) 302.2601.

5.1.14. Hydrolysis of 21/22 with *p*-TsOH/acetone/H_2O: 18a-homo-15-nor-*ent*-halima-1(10),13-dien-18-al (23). To a solution of 0.03 M of the aducts **21/22** (436 mg, 1.44 mmol) in acetone (47 mL) and water (1 mL), *p*-TsOH (82 mg, 0.43 mmol) was added at room temperature. After being stirred for 3 h, the reaction mixture was diluted with water and extracted with Et_2O. The extracts were washed with saturated aqueous $NaHCO_3$ solution and brine. Evaporation of the solvent followed by chromatography on silica gel (Hex/EtOAc 98:2)

yielded **23** (376 mg, 91%). $[\alpha]_D^{22}$ + 47.3 (*c* 0.75, $CHCl_3$); IR (film, cm^{-1}) 3071, 2930, 2728, 1721, 1647, 1458, 1379, 883; ^1H NMR (200 MHz, $CDCl_3$) δ 9.88 (1H, t, *J* = 3.2 Hz, H-18), 5.37 (1H, t, *J* = 3.4 Hz, H-1), 4.66 (2H, br s, H-14), 2.39 (1H, dd, *J* = 14.8 and 3.2 Hz, H_A-18a), 2.22 (1H, dd, *J* = 14.8 and 3.2 Hz, H_B-18a), 1.70 (3H, s, Me-16), 2.13–1.18 (14H, m), 1.03 (3H, s, Me-20), 0.92 (3H, s, Me-19), 0.81 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.1 (C-1), 22.9 (C-2), 30.9 (C-3), 35.1 (C-4), 42.7 (C-5), 23.6 (C-6), 29.2 (C-7), 39.4 (C-8), 43.3 (C-9), 141.4 (C-10), 37.5 (C-11), 32.7 (C-12), 147.2 (C-13), 109.5 (C-14), 23.0 (C-16), 15.8 (C-17), 52.8 (C-18a), 204.3 (C-18), 24.1 (C-19), 22.4 (C-20); EIMS [*m*/*z* (%)] 288 (M^+, 5), 273 (11), 245 (16), 219 (30), 176 (100), 105 (38), 69 (28); HREIMS calcd for $C_{20}H_{32}O$ (M^+) 288.2453, found (M^+) 288.2443.

5.1.15. Oxidation of 16 with TPAP: 16(13 → 14)abeo-*ent*-halima-1(10),14-dien-18-al (24). Oxidation of **16** (429 mg, 1.48 mmol) (as described before for compound **20**) yields after column chromatography over silica gel (Hex/EtOAc 98:2) compound **24** (411 mg, 96%). $[\alpha]_D^{22}$ + 49.2 (*c* 0.89, $CHCl_3$); IR (film, cm^{-1}) 3073, 2936, 2695, 1726, 1649, 1462, 1379, 885; ^1H NMR (200 MHz, $CDCl_3$) δ 9.41 (1H, s, H-18), 5.33 (1H, td, *J* = 3.8 and 1.6 Hz, H-1), 4,65 (2H, br s, H-15), 2.58–2.33 (2H, m), 1.68 (3H, s, Me-16), 2.12–1.03 (14H, m), 0.95 (3H, s, Me-19), 0.89 (3H, s, Me-20), 0.78 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C **NMR** (50 MHz, $CDCl_3$) δ 120.1 (C-1), 22.4 (C-2), 28.7 (C-3), 48.1 (C-4), 36.2 (C-5), 23.2 (C-6), 28.0 (C-7), 38.7 (C-8), 43.2 (C-9), 141.5 (C-10), 39.0 (C-11), 22.2 (C-12), 38.7 (C-13), 146.3 (C-14), 110.0 (C-15), 22.7 (C-16), 15.7 (C-17), 206.6 (C-18), 17.4 (C-19), 22.6 (C-20); EMIE [*m*/*z* (%)] 288 (M^+, 2), 259 (40), 221 (81), 175 (100), 135 (46), 105 (55); HREIMS calcd for $C_{20}H_{32}O$ (M^+) 288.2453, found (M^+) 288.2457.

5.1.16. Reaction of 24 with $MeOCH_3PPh_3$/NaHMDS: 18-methoxy-16(13 → 14)abeo-18a-homo-*ent*-halima-1 (10), 14,18a(18)*Z*-triene (25). Reaction of **24** (397 mg, 1.38 mmol) with $MeOCH_3PPh_3$/NaHMDS (as described before for compounds **21**/**22**) yields after column chromatography over silica gel (Hex/EtOAc 98:2) compound **25** (397 mg, 91%). $[\alpha]_D^{22}$ + 44.8 (*c* 0.66, $CHCl_3$); IR (film, cm^{-1}) 3073, 2932, 1659, 1454, 1377, 1285, 1204, 1105, 885; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (1H, d, *J* = 7.0 Hz, H-18) 5.31 (1H, t, *J* = 3.6 Hz, H-1), 4.68 (1H, br s, H_A-15), 4.65 (1H, br s, H_B-15), 4.13 (1H, d, *J* = 7.0 Hz, H-18a), 3.51 (3H, s, –O*Me*), 1.96 (2H, t, *J* = 7.4 Hz, H-13), 1.70 (3H, s, Me-16), 2.14-1.11 (14H, m), 1.08 (3H, s, Me-19), 0.89 (3H, s, Me-20), 0.80 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.8 (C-1), 23.2 (C-2), 31.2 (C-3), 36.2 (C-4), 43.1 (C-5), 23.3 (C-6), 29.0 (C-7), 38.9 (C-8), 42.9 (C-9), 142.0 (C-10), 39.0 (C-11), 22.0 (C-12), 38.7 (C-13), 146.3 (C-14), 109.5 (C-15), 22.3 (C-16), 15.6 (C-17), 116.3 (C-18a), 145.3 (C-18), 22.8 (C-19), 22.3 (C-20), 59.5 (–O*Me*); EMIE [*m*/*z* (%)] 316 (M^+, 7), 279 (5), 256 (15), 221 (26), 175 (23), 153 (22), 129 (13), 98 (100), 69 (67); HREIMS calcd for $C_{22}H_{36}O$ (M^+) 316.2766, found (M^+) 316.2762.

5.1.17. Hydrolysis of 25 with *p*-TsOH/acetone/H_2O: 16(13 → 14)abeo-18a-homo-*ent*-halima-1(10),14-dien-18-al (26). Hydrolysis of **25** (312 mg, 0.99 mmol) (as described before for compound **23**) yields after column chromatography over silica gel (Hex/EtOAc 98:2) compound **26** (286 mg, 96%). $[\alpha]_D^{22}$ + 53.9 (*c* 0.99, $CHCl_3$); IR (film, cm^{-1}) 3073, 2728, 1723, 1649, 1462, 1379, 885; ^1H NMR (200 MHz, $CDCl_3$) δ 9.86 (1H, t, *J* = 3.2 Hz, H-18), 5.34 (1H, t, *J* = 3.6 Hz, H-1), 4.65 (1H, s, H_A-15), 4,63 (1H, s, H_B-15), 2.35 (1H, dd, *J* = 14.8 and 3.2 Hz, H_A-18a), 2.21 (1H, dd, *J* = 14.8 and 3.2 Hz, H_B-18a), 1.93 (2H, t, *J* = 7.4 Hz, H-13), 1.67 (3H, s, Me-16), 2.15–1.04 (14H, m), 1.01 (3H, s, Me-20), 0.89 (3H, s, Me-19), 0.78 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 119.7 (C-1), 22.6 (C-2), 31.1 (C-3), 35.1 (C-4), 42.5 (C-5), 23.5 (C-6), 29.2 (C-7), 39.2 (C-8), 43.3 (C-9), 141.8 (C-10), 38.9 (C-11), 22.4 (C-12), 38.8 (C-13), 146.2 (C-14), 110.0 (C-15), 22.6 (C-16), 15.7 (C-17), 52.8 (C-18a), 204.1 (C-18), 24.0 (C-19), 22.5 (C-20); EMIE [*m*/*z* (%)] 302 (M^+, 1), 279 (7), 259 (11), 221 (100), 175 (42), 149 (22), 105 (19), 69 (20); HREIMS calcd for $C_{21}H_{34}O$ (M^+) 302.2610, found (M^+) 302.2603.

5.1.18. Hydrolysis of 25 with *p*-TsOH/acetone/H_2O: 16(13 → 14)abeo-18a-homo-1,18-cyclo-*ent*-halima-5(10), 14-dien-18*S*-ol (27) and 16(13 → 14)abeo-18a-homo-1,18-cyclo-*ent*-halima-5(10),14-dien-18*R*-ol (28). To a solution 0.14 M of **25** (45 mg, 0.14 mmol) in acetone (1 mL) and water (2 drops), *p*-TsOH (27 mg, 0.14 mmol) was added at room temperature. After being stirred overnight, the reaction mixture was diluted with water and extracted with Et_2O. The extracts were washed with 6% aqueous $NaHCO_3$ solution and brine. Evaporation of the solvent followed by chromatography on silica gel (Hex/EtOAc 98:2) yielded **27** (28 mg, 65%) and **28** (13 mg, 30%). *Compound* **27**: $[\alpha]_D^{22}$ + 7.1 (*c* 0.95, $CHCl_3$); IR (film, cm^{-1}) 3455, 3075, 2932, 1649, 1462, 1377, 1063, 1040, 885; ^1H NMR (200 MHz, $CDCl_3$) δ 4.66 (2H, br s, H-15), 3.86 (1H, dt, *J* = 8.8 and 3.4 Hz, H-18), 2.68 (1H, dd, *J* = 5.4 and 3.4 Hz, H-1), 1.69 (3H, s, Me-16), 2.17-1.06 (17H, m), 1.03 (3H, s, Me-19), 0.86 (3H, s, Me-20), 0.80 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.5 (C-1), 25.2 (C-2), 32.8 (C-3), 36.7 (C-4), 138.4 (C-5), 22.5 (C-6), 26.6 (C-7), 32.4 (C-8), 38.8 (C-9), 137.9 (C-10), 39.4 (C-11), 21.5 (C-12), 38.8 (C-13), 146.6 (C-14), 109.9 (C-15), 22.7 (C-16), 15.5 (C-17), 47.6 (C-18a), 71.1 (C-18), 22.6 (C-19), 21.5 (C-20); EMIE [*m*/*z* (%)] 302 (M^+, 6), 256 (4), 219 (100), 173 (30), 105 (23), 69 (48); HREIMS calcd for $C_{21}H_{34}O$(M^+) 302.2610, found (M^+) 302.2616. *Compound* **28**: $[\alpha]_D^{22}$ + 44.4 (*c* 0.87, $CHCl_3$); IR (film, cm^{-1}) 3374, 3075, 2932, 1651, 1462, 1377, 1294, 1115, 1038, 1003, 972, 885; ^1H NMR (200 MHz, $CDCl_3$) δ 4.67 (1H, br s, H_A-15), 4.63 (1H, br s, H_B-15), 3.79 (1H, dt, *J* = 8.6 and 3.4 Hz, H-18), 2.56 (1H, dd, *J* = 5.4 and 3.4 Hz, H-1), 1.69 (3H, s, Me-16), 1.00 (3H, s, Me-19), 2.17-0.85 (17H, m), 0.81 (3H, d, *J* = 7.0 Hz, Me-17), 0.80 (3H, s, Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.3 (C-1), 23.4 (C-2), 34.4 (C-3), 37.1 (C-4), 138.7 (C-5), 23.1 (C-6), 27.5 (C-7), 33.0 (C-8), 40.1 (C-9), 140.1 (C-10), 38.9 (C-11), 20.7 (C-12), 37.5 (C-13), 146.4 (C-14), 110.0 (C-15), 22.8 (C-16), 15.9 (C-17), 45.2 (C-

18a), 69.9 (C-18), 22.7 (C-19), 21.5 (C-20); EMIE [*m*/*z* (%)] 302 (M^+, 6), 219 (100), 176 (13), 145 (8), 105 (22), 69 (39); HREIMS calcd for $C_{21}H_{34}O(M^+)$ 302.2610, found (M^+) 302.2615.

5.1.19. Oxidation of 27/28 with TPAP: 16(13 → 14)abeo-18a-homo-1,18-cyclo-*ent*-halima-5(10),14-dien-18-one (29). Oxidation of **27/28** (38 mg, 0.13 mmol) (as described before for compound **20**) yields after column chromatography over silica gel (Hex/EtOAc 97:3) compound **29** (36 mg, 95%). $[\alpha]_D^{22}$ + 294.9 (*c* 0.95, $CHCl_3$); IR (film, cm^{-1}) 3073, 2934, 1724, 1649, 1462, 1379, 1215, 885; ^1H NMR (200 MHz, $CDCl_3$) δ 4.65 (2H, br s, H-15), 3.13 (1H, t, *J* = 2.6 Hz, H-1), 1.67 (3H, s, Me-16), 1.17 (3H, s, Me-19), 2.22-1.06 (17H, m), 0.83 (3H, d, *J* = 7.0 Hz, Me-17), 0.80 (3H, s, Me-20); ^{13}C NMR (50 MHz, $CDCl_3$) δ 49.2 (C-1), 25.4 (C-2), 33.4 (C-3), 39.9 (C-4), 137.6 (C-5), 24.2 (C-6), 27.5 (C-7), 33.1 (C-8), 40.2 (C-9), 141.3 (C-10), 38.5 (C-11), 22.5 (C-12), 36.7 (C-13), 146.5 (C-14), 119.9 (C-15), 22.5 (C-16), 16.0 (C-17), 48.6 (C-18a), 214.0 (C-18), 21.8 (C-19), 21.5 (C-20); EMIE [*m*/*z* (%)] 300 (M^+, 3), 219 (45), 217 (100), 189 (15), 95 (9), 56 (17); HREIMS calcd for $C_{21}H_{32}O$ (M^+) 300.2453, found (M^+) 300.2449.

5.1.20. Oxidation of 18 with TPAP: 15-methoxy-*ent*-halima-1(10),13*E*-dien-18-al (30). Oxidation of **18** (167 mg, 0.52 mmol) (as described before for compound **20**) yields after column chromatography over silica gel (Hex/EtOAc 95:5) compound **30** (158 mg, 95%). IR (film, cm^{-1}) 2930, 2695, 1726, 1464, 1379, 1107; ^1H NMR (200 MHz, $CDCl_3$) δ 9.41 (1H, s, H-18), 5.42–5.27 (2H, m, H-1 y H-14), 3.90 (2H, d, *J* = 7.0 Hz, H-15), 3.30 (3H, s, –O*Me*), 2.49–2.31 (1H, m, H-5), 1.67 (3H, s, Me-16), 2.20–1.16 (13H, m), 0.95 (3H, s, Me-19), 0.90 (3H, s, Me-20), 0.79 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (50 MHz, $CDCl_3$) δ 120.2 (C-1), 22.2 (C-2), 28.4 (C-3), 47.8 (C-4), 36.0 (C-5), 23.0 (C-6), 27.6 (C-7), 38.6 (C-8), 43.0 (C-9), 141.1 (C-10), 37.6 (C-11), 34.0 (C-12), 141.1 (C-13), 120.3 (C-14), 69.0 (C-15), 16.6 (C-16), 15.4 (C-17), 205.7 (C-18), 17.2 (C-19), 22.2 (C-20), 57.6 (–O*Me*); EMIE [*m*/*z* (%)] 318 (M^+, 2), 286 (23), 257 (66), 240 (60), 205 (70), 177 (100), 161 (41), 145 (32), 10 (68), 91 (75), 77 (80); HREIMS calcd for $C_{21}H_{34}O_2$ (M^+) 318.2559, found (M^+) 318.2564.

5.1.21. Reaction of 30 with $MeOCH_3$ PPh_3/NaHMDS: 15,18-dimethoxy-18a-homo-*ent*-halima-1(10),13*E*, 18a(18)*Z*-triene (31) and 15,18-dimethoxy-18a-homo-*ent*-halima-1(10),13*E*,18a(18)*E*-triene (32). Reaction of **30** (141 mg, 0.44 mmol) with $MeOCH_3PPh_3$/NaHMDS (as described before for compounds **21/22**) yields after column chromatography over silica gel (Hex/EtOAc 98:2) compounds **31** (127 mg, 83%) and **32** (16 mg, 10%) (93%, *Z*/*E*: 8:1). *Compound* **31:** $[\alpha]_D^{22}$ + 61.0 (*c* 0.73, $CHCl_3$); IR (film, cm^{-1}) 3073, 2930, 1657, 1456, 1379, 1105, 957, 725; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (1H, d, *J* = 7.0 Hz, H-18), 5.36–5.28 (2H, m, H-1 and H-14), 4.13 (1H, d, *J* = 7.0 Hz, H-18a), 3.91 (2H, d, *J* = 6.7 Hz, H-15), 3.51 (3H, s, =CHO*Me*), 3.32 (3H, s, –CH_2O*Me*), 1.65 (3H, s, Me-16), 2.10–1.18 (14H, m), 1.07 (3H, s, Me-19), 0.90 (3H, s, Me-20), 0.80 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.9 (C-1), 23.1 (C-2), 31.3 (C-3), 36.2 (C-4), 43.2 (C-5), 23.3 (C-6), 28.9 (C-7), 39.0 (C-8), 42.8 (C-9), 141.8 (C-10), 37.6 (C-11), 34.2 (C-12), 141.6 (C-13), 120.3 (C-14), 69.0 (C-15), 16.6 (C-16), 15.6 (C-17), 116.3 (C-18a), 145.3 (C-18), 22.8 (C-19), 22.2 (C-20), 57.7 (–CH_2O*Me*), 59.5 (=CHO*Me*); EMIE [*m*/*z* (%)] 346 (M^+, 14), 314 (15), 282 (6), 262 (9), 233 (75), 206 (35), 176 (30), 98 (100), 83 (28); HREIMS calcd for $C_{23}H_{38}O_2$ (M^+) 346.2871, found (M^+) 346.2878. *Compound* **32**: $[\alpha]_D^{22}$ + 24.5 (*c* 0.59, $CHCl_3$); IR (film, cm^{-1}) 3073, 2928, 1647, 1464, 1379, 1209, 1103, 941; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (1H, d, *J* = 13.0 Hz, H-18), 5.39–5.28 (2H, m, H-1 and H-14), 4.85 (1H, d, *J* = 13.0 Hz, H-18a), 3.91 (2H, d, *J* = 6.7 Hz, H-15), 3.48 (3H, s, =CHO*Me*), 3.32 (3H, s, –CH_2O*Me*), 1.66 (3H, s, Me-16), 2.16–1.18 (14H, m), 0.93 (3H, s, Me-19), 0.92 (3H, s, Me-20), 0.80 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.9 (C-1), 22.3 (C-2), 34.6 (C-3), 34.8 (C-4), 43.3 (C-5), 22.9 (C-6), 28.5 (C-7), 38.4 (C-8), 42.6 (C-9), 141.6 (C-10), 37.7 (C-11), 34.6 (C-12), 141.4 (C-13), 120.0 (C-14), 69.0 (C-15), 16.7 (C-16), 15.6 (C-17), 119.9 (C-18a), 145.5 (C-18), 22.5 (C-19), 22.5 (C-20), 57.8 (–CH_2O*Me*), 55.8 (=CHO*Me*); EMIE [*m*/*z* (%)] 346 (M^+, 12), 314 (14), 282 (7), 262 (8), 233 (70), 206 (35), 176 (34), 98 (100), 83 (39); HREIMS calcd for $C_{23}H_{38}O_2$ (M^+) 346.2871, found (M^+) 346.2881.

5.1.22. Hydrolysis of 31/32 with *p*-TsOH/acetone/H_2O: 15-methoxy-18a-homo-1,18-cyclo-*ent*-halima-5(10),13*E*-dien-18*S*-ol (33) and 15-methoxy-18a-homo-1,18-cyclo-*ent*-halima-5(10),13*E*-dien-18 R-ol (34). Hydrolysis of **31/32** (134 mg, 0.39 mmol) (as described before for compounds **27/28**) yields after column chromatography over silica gel (Hex/EtOAc 98:2) compounds **33** (73 mg, 57%) and **34** (43 mg, 33%). *Compound* **33**: $[\alpha]_D^{22}$ − 8.8 (*c* 0.70, $CHCl_3$); IR (film, cm^{-1}) 3453, 2928, 1670, 1456, 1377, 1101, 1069, 953, 910; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, t, *J* = 6.8 Hz, H-14), 3.89 (2H, d, *J* = 6.8 Hz, H-15), 3.89-3.83 (1H, m, H-18), 3.30 (3H, s, –O*Me*), 2.68–2.62 (1H, m, H-1), 1.65 (3H, s, Me-16), 1.03 (3H, s, Me-19), 0.88 (3H, s, Me-20), 2.09–0.80 (15H, m), 0.80 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.3 (C-1), 24.9 (C-2), 32.5 (C-3), 36.4 (C-4), 138.0 (C-5), 21.2 (C-6), 26.3 (C-7), 32.1 (C-8), 38.5 (C-9), 137.5 (C-10), 37.4 (C-11), 33.8 (C-12), 141.4 (C-13), 120.0 (C-14), 69.0 (C-15), 16.7 (C-16), 15.1 (C-17), 47.0 (C-18a), 70.7 (C-18), 22.3 (C-19), 21.3 (C-20), 57.8 (–O*Me*); EMIE [*m*/*z* (%)] 333 (M^++1, 2), 289 (5), 219 (100), 173 (36), 128 (18), 105 (16), 91 (19). *Compound* **34**: $[\alpha]_D^{22}$ + 25.0 (*c* 0.28, $CHCl_3$); IR (film, cm^{-1}) 3443, 2934, 1653, 1458, 1113; ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, t, *J* = 6.8 Hz, H-14), 3.91 (2H, d, *J* = 6.8 Hz, H-15), 3.87–3.80 (1H, m, H-18), 3.32 (3H, s, –O*Me*), 2.57–2.52 (1H, m, H-1), 1.66 (3H, s, Me-16), 1.01 (3H, s, Me-19), 2.16–0.94 (15H, m) 0.83 (3H, s, Me-20), 0.82 (3H, d, *J* = 7.0 Hz, Me-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1 (C-1), 20.4 (C-2), 34.2 (C-3), 36.8 (C-4), 138.7 (C-5), 23.0 (C-6), 27.2 (C-7), 32.6 (C-8), 39.8 (C-9), 139.5 (C-10), 35.9 (C-11), 34.6 (C-12), 141.2 (C-13), 120.0 (C-14), 69.0 (C-15), 16.7 (C-16), 15.5 (C-17), 44.7 (C-18a), 69.5 (C-18), 22.6 (C-

19), 21.3 (C-20), 57.8 (–O*Me*); EMIE [*m*/*z* (%)] 332 (M^+,1), 288 (6), 219 (100), 176 (52), 145 (18), 105 (29).

5.1.23. Oxidation of 33/34 with TPAP: 15-methoxy-18a-homo-1,18-cyclo-*ent*-halima-5(10),13*E*-dien-18-ona (35). Oxidation of **33/34** (89 mg, 0.28 mmol) (as described before for compound **20**) yields after column chromatography over silica gel (Hex/EtOAc 9:1) compound **35** (78 mg, 88%). $[\alpha]_D^{22}$ +228.8 (*c* 0.94, $CHCl_3$); IR (film, cm^{-1}) 2924, 1723, 1674, 1462, 1381, 1217, 1152, 1099, 1028, 955, 918; ^1H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, t, *J* = 6.8 Hz, H-14), 3.90 (2H, d, *J* = 6.8 Hz, H-15), 3.31 (3H, s, –O*Me*), 3.15 (1H, t, *J* = 2.7 Hz, H-1), 1.66 (3H, s, Me-16), 2.18-1.24 (15H, m), 1.17 (3H, s, Me-19), 0.84 (3H, d, *J* = 6.9 Hz, Me-17), 0.82 (3H, s, Me-20); ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.0 (C-1), 25.2 (C-2), 33.1 (C-3), 39.7 (C-4), 137.0 (C-5), 23.8 (C-6), 27.2 (C-7), 32.8 (C-8), 39.9 (C-9), 141.0 (C-10), 35.4 (C-11), 34.0 (C-12), 141.2 (C-13), 120.4 (C-14), 68.9 (C-15), 16.4 (C-16), 15.6 (C-17), 48.4 (C-18a), 213.5 (C-18), 21.5 (C-19), 21.4 (C-20), 57.7 (–O*Me*); EMIE [*m*/*z* (%)] 330 (M^+, 1), 217 (75), 189 (23), 161 (12), 105 (44), 77 (100).

5.1.24. Reaction of 23 with 3-bromofuran/*n*-BuLi: 1,25-epoxy-18-nor-*ent*-isodysidiola-1,3(25),9,19-tetraen-4*S*-ol (36) and 1,25-epoxy-18-nor-*ent*-isodysidiola-1,3(25),9,19-tetraen-4*R*-ol (37). A solution of 3-bromofuran (1 mL, 11.12 mmol) in THF (12 mL) was treated dropwise with 1.6 M in hexane *n*-BuLi (6.9 mL, 11.04 mmol) at −78 °C. After the reaction mixture was stirred for 30 min at this temperature, a solution of **23** (311 mg, 1.08 mmol) in dry THF (10 mL) was added and stirred for an additional 30 min. The reaction mixture was treated with saturated aqueous NH_4Cl solution, warmed to room temperature and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The residue obtained after solvent removal was purified by chromatography (Hex/benzene 2:8) to yield **37** (188 mg, 49%) and **36** (154 mg, 40%). *Compound* **37**: $[\alpha]_D^{22}$ +10.6 (*c* 1.34, $CHCl_3$); IR (film, cm^{-1}) 3418, 3071, 2932, 1649, 1454, 1377, 1024, 878, 795; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s, H-1), 7.35 (1H, s, H-25), 6.40 (1H, s, H-2), 5.37 (1H, t, *J* = 3.4 Hz, H-9), 4.88–4.83 (1H, m, H-4) 4.65 (1H, s, H_A-20), 4.62 (1H, s, H_B-20), 1.68 (3H, s, Me-21), 2.18–1.23 (16H, m), 0.92 (3H, s, Me-22), 0.89 (3H, s, Me-24), 0.82 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3 (C-1), 108.5 (C-2), 131.1 (C-3), 64.1 (C-4), 47.7 (C-5), 34.2 (C-6), 31.8 (C-7), 22.8 (C-8), 120.0 (C-9), 141.3 (C-10), 42.4 (C-11), 22.9 (C-12), 28.9 (C-13), 38.8 (C-14), 42.8 (C-15), 37.4 (C-16), 32.4 (C-17), 147.2 (C-19), 109.0 (C-20), 22.7 (C-21), 22.3 (C-22), 15.6 (C-23), 22.7 (C-24), 138.4 (C-25); EIMS [*m*/*z* (%)] 356 (M^+, 2), 338 (10), 269 (42), 244 (23), 176 (100), 105 (27); HREIMS calcd for $C_{24}H_{36}O_2$ (M^+) 356.2715, found (M^+) 356.2709. *Compound* **36**: $[\alpha]_D^{22}$ +52.7 (*c* 0.49, $CHCl_3$); IR (film, cm^{-1}) 3418, 3071, 2932, 1649, 1454, 1377, 1024, 878, 795; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s, H-1), 7.35 (1H, s, H-25), 6.39 (1H, s, H-2), 5.34 (1H, t, *J* = 3.4 Hz, H-9), 4.88-4.83 (1H, m, H-4) 4.65 (1H, s, H_A-20), 4.64 (1H, s, H_B-20), 1.70 (3H, s, Me-21), 2.14-1.23 (16H, m), 0.99 (3H, s, Me-22), 0.90 (3H, s, Me-24), 0.82 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3 (C-1), 108.5 (C-2), 131.1 (C-3), 64.1 (C-4), 47.4 (C-5), 34.0 (C-6), 31.3 (C-7), 22.7 (C-8), 119.7 (C-9), 141.7 (C-10), 42.1 (C-11), 23.1 (C-12), 28.9 (C-13), 38.9 (C-14), 42.9 (C-15), 37.2 (C-16), 32.3 (C-17), 147.3 (C-19), 108.9 (C-20), 22.8 (C-21), 22.2 (C-22), 15.6 (C-23), 23.3 (C-24), 138.4 (C-25); EIMS [*m*/*z* (%)] 356 (M^+, 2), 338 (11), 269 (44), 244 (25), 177 (100), 105 (28); HREIMS calcd for $C_{24}H_{36}O_2$ (M^+) 356.2715, found (M^+) 356.2713.

5.1.25. Reaction of acetylation of 37: 4*R*-acetoxy-1,25-epoxy-18-nor-ent-isodysidiola-1,3(25),9,19-tetraene (38). Acetylation of **37** (24 mg, 0.067 mmol) (as described before for compound **12**) yields compound **38** (26 mg, 97%). $[\alpha]_D^{22}$ +1.1 (*c* 0.92, $CHCl_3$); IR (film, cm^{-1}) 3073, 2930, 1740, 1456, 1373, 1235, 1024, 945, 876, 797; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39 (1H, s, H-25), 7.32 (1H, s, H-1), 6.38 (1H, s, H-2), 5.98 (1H, dd, *J* = 9.2 and 3.6 Hz, H-4), 5.37 (1H, t, *J* = 3.4 Hz, H-9), 4.64 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 2.01 (3H, s, –OOC*Me*), 1.68 (3H, s, Me-21), 2.22-1.12 (16H, m), 0.92 (3H, s, Me-22), 0.85 (3H, s, Me-24), 0.82 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.3 (C-1), 109.1 (C-2), 126.9 (C-3), 65.7 (C-4), 44.3 (C-5), 34.5 (C-6), 31.4 (C-7), 23.0 (C-8), 120.2 (C-9), 141.5 (C-10), 42.6 (C-11), 23.4 (C-12), 29.2 (C-13), 39.1 (C-14), 43.1 (C-15), 37.5 (C-16), 32.6 (C-17), 147.4 (C-19), 109.3 (C-20), 23.1 (C-21), 22.6 (C-22), 15.6 (C-23), 23.1 (C-24), 140.3 (C-25), 170.6 (–O*OC*Me), 21.7 (–OOC*Me*); EIMS [*m*/*z* (%)] 398 (M^+, 1), 338 (21), 269 (62), 244 (27), 176 (100), 149 (20), 105 (27); HREIMS calcd for $C_{26}H_{38}O_3$(M^+) 398.2821, found (M^+) 398.2812.

5.1.26. Oxidation of 36 with $^1O_2$: 4*S*, 25-dihydroxy-18-nor-*ent*-isodysidiola-2,9,19-trien-1,25-olide (2a). Rose Bengal (6 mg) was added to a solution of **36** (20 mg, 0.056 mmol) and DIPEA (100 μL, 0.574 mmol) in dry CH_2Cl_2 (10 mL) at room temperature. Anhydrous oxygen was bubbled in for 10 min and after that, the solution was placed under oxygen atmosphere at −78 °C and irradiated with a 200 W lamp. After 4 h irradiation was stopped, the pink solution was allowed to warm to room temperature, and saturated aqueous oxalic acid (5 mL) was added. After 30 min of vigorous stirring, the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give a residue which was purified by silica gel column chromatography (Hex/EtOAc 8:2) to yield **2a** (18 mg, 83%). Spectroscopic and physical data for the mixture of α and β epimers at C_{20}. $[\alpha]_D^{22}$ +68.0 (*c* 0.25, $CHCl_3$); IR (film, cm^{-1}) 3401, 3073, 2934, 1748, 1647, 1456, 1379, 1134, 953, 885; EIMS [*m*/*z* (%)] 388 (M^+, 1), 295 (8), 252 (10), 225 (7), 97 (47); HREIMS calcd for $C_{24}H_{36}O_4$ (M^+) 388.2614, found (M^+) 388.2608. Major component: ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (1H, br s, H-25), 6.04 (1H, s, H-2), 5.37 (1H, t, *J* = 3.4 Hz, H-9), 4.88–4.76 (1H, m, H-4), 4.67 (1H, s, H_A-20), 4.64 (1H, s, H_B-20), 2.13 and 1.98 (1H, m ea, H-8), 1.98 and 1.36 (1H, m ea, H-13), 1.97 and 1.30 (1H, m ea, H-16), 1.96 (1H, m H-11),

1.89 and 1.70 (1H, m ea, H-17), 1.70 (3H, s, Me-21), 1.62 (2H, m, H-5), 1.59 (1H, m, H-14), 1.55 and 1.27 (1H, m ea, H-12), 1.42 and 1.30 (1H, m ea, H-7), 1.02 (3H, s, Me-24), 0.92 (3H, s, Me-22), 0.82 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C-1), 117.2 (C-2), 169.8 (C-3), 65.9 (C-4), 45.2 (C-5), 34.4 (C-6), 31.1 (C-7), 22.5 (C-8), 119.6 (C-9), 141.6 (C-10), 42.2 (C-11), 23.2 (C-12), 28.9 (C-13), 38.8 (C-14), 43.0 (C-15), 37.2 (C-16), 32.4 (C-17), 147.2 (C-19), 109.1 (C-20), 22.8 (C-21), 22.1 (C-22), 15.6 (C-23), 23.3 (C-24), 97.0 (C-25). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, br s, H-25), 5.94 (1H, s, H-2), 5.37 (1H, t, J = 3.4 Hz, H-9), 4.88-4.76 (1H, m, H-4), 4.67 (1H, s, H_A-20), 4.64 (1H, s, H_B-20), 2.13 and 1.98 (1H, m ea, H-8), 1.98 and 1.36 (1H, m ea, H-13), 1.97 and 1.30 (1H, m ea, H-16), 1.96 (1H, m H-11), 1.89 and 1.70 (1H, m ea, H-17), 1.70 (3H, s, Me-21), 1.62 (2H, m, H-5), 1.59 (1H, m, H-14), 1.55 and 1.27 (1H, m ea, H-12), 1.42 and 1.30 (1H, m ea, H-7), 1.01 (3H, s, Me-24), 0.92 (3H, s, Me-22), 0.82 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0 (C-1), 117.6 (C-2), 169.8 (C-3), 65.5 (C-4), 44.8 (C-5), 34.2 (C-6), 29.6 (C-7), 22.6 (C-8), 119.6 (C-9), 141.6 (C-10), 42.2 (C-11), 23.3 (C-12), 28.9 (C-13), 38.8 (C-14), 43.0 (C-15), 37.2 (C-16), 32.4 (C-17), 147.3 (C-19), 109.1 (C-20), 22.8 (C-21), 22.1 (C-22), 15.6 (C-23), 23.3 (C-24), 97.3 (C-25).

5.1.27. Oxidation of 37 with $^1O_2$: 4*R*, 25-dihydroxy-18-nor-*ent*-isodysidiola-2,9,19-trien-1,25-olide (2b). Oxidation of **37** (26 mg, 0.073 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 8:2) compound **2b** (24 mg, 85%). Spectroscopic and physical data for the mixture of α and β epimers at $C_{20.}$ $[\alpha]_D^{22}$ + 22.3 (*c* 1.09, $CHCl_3$); IR (film, cm^{-1}) 3401, 3073, 2934, 1748, 1647, 1456, 1379, 1134, 953, 885; EIMS [*m*/*z* (%)] 388 (M^+, 1), 301 (10), 256 (20), 213 (11), 153 (53), 107 (38), 69 (100); HREIMS calcd for $C_{24}H_{36}O_4$(M^+) 388.2614, found (M^+) 388.2608. Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (1H, s, H-2), 6.03 (1H, br s, H-25), 5.39 (1H, t, J = 3.6 Hz, H-9), 4.83–4.75 (1H, m, H-4), 4.68 (1H, s, H_A-20), 4.64 (1H, s, H_B-20), 1.71 (3H, s, Me-21), 2.17–1.15 (16H, m), 0.95 (3H, s, Me-24), 0.92 (3H, s, Me-22), 0.82 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C-1), 117.0 (C-2), 170.7 (C-3), 65.7 (C-4), 45.6 (C-5), 34.7 (C-6), 31.9 (C-7), 22.7 (C-8), 120.0 (C-9), 141.2 (C-10), 42.2 (C-11), 23.0 (C-12), 28.7 (C-13), 38.5 (C-14), 42.8 (C-15), 37.3 (C-16), 32.4 (C-17), 147.5 (C-19), 109.1 (C-20), 22.8 (C-21), 22.2 (C-22), 15.6 (C-23), 22.8 (C-24), 97.6 (C-25). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, br s, H-25), 5.93 (1H, s, H-2), 5.37 (1H, t, J = 3.6 Hz, H-9), 4.78–4.69 (1H, m, H-4), 4.68 (1H, s, H_A-20), 4.64 (1H, s, H_B-20), 1.70 (3H, s, Me-21), 2.17–1.15 (16H, m), 0.93 (3H, s, Me-24), 0.92 (3H, s, Me-22), 0.82 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (C-1), 117.4 (C-2), 170.4 (C-3), 65.3 (C-4), 44.8 (C-5), 34.4 (C-6), 31.2 (C-7), 22.7 (C-8), 119.6 (C-9), 141.6 (C-10), 42.2 (C-11), 23.0 (C-12), 28.9 (C-13), 38.7 (C-14), 43.0 (C-15), 37.2 (C-16), 32.4 (C-17), 147.2 (C-19), 109.1 (C-20), 22.8 (C-21), 22.2 (C-22), 15.6 (C-23), 22.8 (C-24), 97.8 (C-25).

5.1.28. Oxidation of 38 with $^1O_2$: 4*R*-acetoxy-25-hydroxy-18-nor-*ent*-isodysidiola-2,9,19-trien-1,25-olide (1b). Oxidation of **38** (25 mg, 0.063 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 85:15) compound **1b** (24 mg, 89%). Spectroscopic and physical data for the mixture of α and β epimers at $C_{20.}$ $[\alpha]_D^{22}$ + 1.2 (*c* 0.97, $CHCl_3$); IR (film, cm^{-1}) 3380, 3081, 2934, 1750, 1653, 1458, 1375, 1260, 1227, 1127, 1030, 957, 885; EIMS [*m*/*z* (%)] 430 (M^+, 2), 256 (18), 205 (14), 171 (70), 97 (56); HREIMS calcd for $C_{26}H_{38}O_5$ (M^+) 430.2719, found (M^+) 430.2713. Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98–5.95 (1H, m, H-25), 5.94 (1H, s, H-2), 5.50 (1H, d, J = 9.0 Hz, H-4), 5.39 (1H, t, J = 3.6 Hz, H-9), 4.68 (1H, br s, H_A-20), 4.63 (1H, br s, H_B-20), 2.11 (3H, s, –OOC*Me*), 2.10 and 1.52 (1H, m ea, H-8), 2.06 and 1.47 (1H, m ea, H-5), 1.99 and 1.84 (1H, m ea, H-13), 1.87 and 1.22 (1H, m ea, H-17), 1.86 and 1.38 (1H, m ea, H-16), 1.84 (1H, m, H-11), 1.72 (2H, m, H-12), 1.70 (3H, s, Me-21), 1.61 (1H, m, H-14), 1.25 and 1.12 (1H, m ea, H-7), 0.93 (3H, s, Me-22), 0.90 (3H, s, Me-24), 0.82 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (C-1), 118.0 (C-2), 168.2 (C-3), 67.1 (C-4), 43.1 (C-5), 34.7 (C-6), 31.3 (C-7), 22.6 (C-8), 119.9 (C-9), 141.2 (C-10), 42.1 (C-11), 22.9 (C-12), 28.7 (C-13), 38.3 (C-14), 42.8 (C-15), 37.2 (C-16), 32.4 (C-17), 147.1 (C-19), 109.2 (C-20), 22.8 (C-21), 22.2 (C-22), 15.6 (C-23), 22.5 (C-24), 97.5 (C-25), 171.0 (–O*OC*Me), 20.9 (–OOC*Me*). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21–6.17 (1H, m, H-25), 5.98 (1H, s, H-2), 5.61 (1H, d, J = 9.0 Hz, H-4), 5.38 (1H, t, J = 3.6 Hz, H-9), 4.68 (1H, br s, H_A-20), 4.63 (1H, br s, H_B-20), 2.10 and 1.52 (1H, m ea, H-8), 2.08 (3H, s, –OOC*Me*), 2.06 and 1.47 (1H, m ea, H-5), 1.99 and 1.84 (1H, m ea, H-13), 1.87 and 1.22 (1H, m ea, H-17), 1.86 and 1.38 (1H, m ea, H-16), 1.84 (1H, m, H-11), 1.72 (2H, m, H-12), 1.70 (3H, s, Me-21), 1.61 (1H, m, H-14), 1.25 and 1.12 (1H, m ea, H-7), 0.93 (3H, s, Me-22), 0.89 (3H, s, Me-24), 0.82 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C-1), 118.8 (C-2), 167.4 (C-3), 66.7 (C-4), 42.6 (C-5), 34.7 (C-6), 31.3 (C-7), 22.6 (C-8), 119.9 (C-9), 141.2 (C-10), 42.2 (C-11), 22.9 (C-12), 28.7 (C-13), 38.5 (C-14), 42.9 (C-15), 37.3 (C-16), 32.4 (C-17), 147.1 (C-19), 109.2 (C-20), 22.8 (C-21), 22.2 (C-22), 15.6 (C-23), 22.5 (C-24), 97.6 (C-25), 170.4 (–O*OC*Me), 20.9 (–OOC*Me*).

5.1.29. Reaction of 26 with 3-bromofuran/*n*-BuLi: 1,25-epoxy-*ent*-isodysidiola-1,3(25),9,19-tetraen-4*S*-ol (39) and 1,25-epoxy-*ent*-isodysidiola-1,3(25),9,19-tetraen-4*R*-ol (41). Reaction of **26** (275 mg, 0.91 mmol) with 3-bromofuran/*n*-BuLi (as described before for compounds **36**/**37**) yields after column chromatography over silica gel (Hex/Benzene 3/7) compounds **39** (141 mg, 42%) and **41** (165 mg, 49%). *Compound* **39**: $[\alpha]_D^{22}$ + 7.3 (*c* 0.89, $CHCl_3$); IR (film, cm^{-1}) 3407, 3073, 2940, 1649, 1503, 1445, 1379, 1161, 1065, 1024, 955, 874, 793, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s, H-1), 7.35 (1H, s, H-25), 6.39 (1H, s, H-2), 5.35 (1H, t, J = 3.7 Hz, H-9), 4.85 (1H, dd, J = 8.2 y 3.5 Hz, H-4), 4.66 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 1.66 (3H, s, Me-21), 2.16–1.03 (18H, m), 0.90 (3H, s, Me-22), 0.88

(3H, s, Me-24), 0.80 (3H, d, $J = 7.0$ Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2 (C-1), 108.6 (C-2), 131.1 (C-3), 64.2 (C-4), 47.7 (C-5), 34.3 (C-6), 31.9 (C-7), 22.8 (C-8), 119.6 (C-9), 141.7 (C-10), 42.4 (C-11), 22.9 (C-12), 28.9 (C-13), 38.6 (C-14), 42.9 (C-15), 38.9 (C-16), 22.0 (C-17), 38.6 (C-18), 146.2 (C-19), 109.6 (C-20), 22.3 (C-21), 22.5 (C-22), 15.6 (C-23), 22.7 (C-24), 138.4 (C-25); EMIE [*m*/*z* (%)] 370 (M^+, 3), 352 (7), 269 (68), 243 (8), 219 (16), 176 (100), 105 (49), 69 (75); HREIMS calcd for $C_{25}H_{38}O_2$ (M^+) 370.2872, found (M^+) 370.2865. *Compound* **41**: $[\alpha]_D^{22}$ +47.2 (*c* 0.89, $CHCl_3$); IR (film, cm^{-1}) 3407, 3073, 2940, 1649, 1503, 1445, 1379, 1161, 1065, 1024, 955, 874, 793, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, s, H-1), 7.34 (1H, s, H-25), 6.39 (1H, s, H-2), 5.32 (1H, t, $J = 3.6$ Hz, H-9), 4.85 (1H, dd, $J = 7.8$ and 3.8 Hz, H-4), 4.66 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 1.67 (3H, s, Me-21), 2.16-1.07 (18H, m), 0.98 (3H, s, Me-24), 0.89 (3H, s, Me-22), 0.80 (3H, d, $J = 7.0$ Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3 (C-1), 108.5 (C-2), 131.1 (C-3), 64.1 (C-4), 47.4 (C-5), 34.1 (C-6), 31.3 (C-7), 22.7 (C-8), 119.3 (C-9), 141.9 (C-10), 42.1 (C-11), 23.0 (C-12), 28.9 (C-13), 38.8 (C-14), 43.0 (C-15), 38.9 (C-16), 22.2 (C-17), 38.6 (C-18), 146.3 (C-19), 109.5 (C-20), 22.4 (C-21), 22.4 (C-22), 15.6 (C-23), 23.3 (C-24), 138.4 (C-25); EMIE [*m*/*z* (%)] 370 (M^+, 2), 352 (8), 269 (70), 243 (7), 219 (14), 176 (100), 105 (47), 69 (77); HREIMS calcd for $C_{25}H_{38}O_2$ (M^+) 370.2872, found (M^+) 370.2868.

5.1.30. Reaction of acetylation of 39: 4*S*-acetate 1,25-epoxy-*ent*-isodysidiola-1,3(25),9,19-tetraenyl (40). Acetylation of **39** (29 mg, 0.078 mmol) (as described before for compound **12**) yields compound **40** (32 mg, 99%). $[\alpha]_D^{22}$ −8.4 (*c* 1.15, $CHCl_3$); IR (film, cm^{-1}) 3073, 2938, 1738, 1649, 1503, 1462, 1371, 1236, 1163, 1024, 943, 874, 797; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, s, H-25), 7.32 (1H, s, H-1), 6.36 (1H, s, H-2), 5.97 (1H, dd, $J = 8.8$ and 3.4 Hz, H-4), 5.34 (1H, t, $J = 3.6$ Hz, H-9), 4.67 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 2.00 (3H, s, –OOC*Me*), 1.67 (3H, s, Me-21), 2.18–1.05 (18H, m), 0.89 (3H, s, Me-22), 0.84 (3H, s, Me-24), 0.80 (3H, d, $J = 7.0$ Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9 (C-1), 108.9 (C-2), 126.7 (C-3), 65.6 (C-4), 44.1 (C-5), 34.2 (C-6), 31.2 (C-7), 22.6 (C-8), 119.5 (C-9), 141.5 (C-10), 42.3 (C-11), 23.1 (C-12), 28.9 (C-13), 38.7 (C-14), 42.9 (C-15), 38.9 (C-16), 22.1 (C-17), 38.5 (C-18), 146.1 (C-19), 109.6 (C-20), 22.4 (C-21), 22.4 (C-22), 15.5 (C-23), 22.8 (C-24), 139.9 (C-25), 170.2 (–O*OC*Me), 21.4 (–OOC*Me*); EMIE [*m*/*z* (%)] 412 (M^+, 1), 353 (22), 270 (88), 177 (100), 97 (62); HREIMS calcd for $C_{27}H_{40}O_3$(M^+) 412.2977, found (M^+) 412.2970.

5.1.31. Reaction of acetylation of 41: 4*R*-acetate 1,25-epoxy-*ent*-isodysidiola-1,3(25),9,19-tetraenyl (42). Acetylation of **41** (33 mg, 0.089 mmol) (as described before for compound **12**) yields compound **42** (36 mg, 98%). $[\alpha]_D^{22}$ +50.4 (*c* 0.99, $CHCl_3$); IR (film, cm^{-1}) 3073, 2938, 1738, 1649, 1503, 1462, 1371, 1236, 1163, 1024, 943, 874, 797; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, s, H-25), 7.33 (1H, s, H-1), 6.36 (1H, s, H-2), 5.96 (1H, dd, $J = 8.8$ and 3.4 Hz, H-4), 5.32 (1H, t, $J = 3.6$ Hz, H-9), 4.67 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 2.01 (3H, s, –OOC*Me*), 1.67 (3H, s, Me-21), 2.18-1.07 (18H, m), 0.89 (3H, s, Me-22), 0.87 (3H, s, Me-24), 0.79 (3H, d, $J = 7.0$ Hz, Me-23) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (C-1), 108.8 (C-2), 126.6 (C-3), 65.7 (C-4), 44.0 (C-5), 34.0 (C-6), 31.1 (C-7), 22.6 (C-8), 119.4 (C-9), 141.6 (C-10), 42.4 (C-11), 22.9 (C-12), 28.9 (C-13), 38.8 (C-14), 42.9 (C-15), 38.9 (C-16), 22.2 (C-17), 38.7 (C-18), 146.2 (C-19), 109.6 (C-20), 22.4 (C-21), 22.4 (C-22), 15.5 (C-23), 22.6 (C-24), 139.9 (C-25), 170.2 (–O*OC*Me), 21.4 (–OOC*Me*); EMIE [*m*/*z* (%)] 412 (M^+, 2), 352 (15), 270 (78), 259 (33), 177 (100), 175 (58), 106 (33); HREIMS calcd for $C_{27}H_{40}O_3$(M^+) 412.2977, found (M^+) 412.2972.

5.1.32. Oxidation of 39 with $^1O_2$: 4*S*,25-dihydroxy-*ent*-isodysidiola-2,9,19-trien-1,25-olide (4a). Oxidation of **39** (32 mg, 0.086 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 8:2) compound **4a** (31 mg, 89%). Spectroscopic and physical data for the mixture of α and β epimers at C_{20}. $[\alpha]_D^{22}$ −5.8 (*c* 0.54, $CHCl_3$); Pf = 127–128 °C; IR (film, cm^{-1}) 3401, 3075, 2934, 1755, 1651, 1462, 1379, 1136, 1071, 953, 889; FABMS [*m*/*z* (%)] 403 (M^++ H, 5), 367 (9), 319 (13), 289 (4), 259 (20), 154 (73), 91 (76); HRFABMS calcd for $C_{25}H_{39}O_4$(M^++H) 403.2848, found (M^++H) 403.2858. Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (1H, br s, H-25), 6.04 (1H, br s, H-2), 5.36 (1H, t, $J = 3.4$ Hz, H-9), 4.83–4.75 (1H, m, H-4), 4.69 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 4.14 (1H, br s, –OH), 2.07 (2H, m, H-8), 1.98 and 1.35 (1H, m ea, H-13), 1.94 (2H, m, H-18), 1.88 (1H, m, H-11), 1.79 and 1.48 (1H, m ea, H-5), 1.75 and 1.20 (1H, m ea, H-16), 1.69 (3H, s, Me-21), 1.57 (1H, m, H-14), 1.55 (2H, m, H-12), 1.53 and 1.42 (1H, m ea, H-7), 1.15 (2H, m, H-17), 0.95 (3H, s, Me-24), 0.91 (3H, s, Me-22), 0.81 (3H, d, $J = 7.0$ Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (C-1), 117.1 (C-2), 170.2 (C-3), 65.8 (C-4), 45.5 (C-5), 34.7 (C-6), 31.7 (C-7), 22.7 (C-8), 119.6 (C-9), 141.5 (C-10), 42.5 (C-11), 22.7 (C-12), 28.9 (C-13), 38.3 (C-14), 42.9 (C-15), 38.8 (C-16), 22.0 (C-17), 38.5 (C-18), 146.6 (C-19), 109.6 (C-20), 22.5 (C-21), 22.5 (C-22), 15.5 (C-23), 22.5 (C-24), 97.2 (C-25). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (1H, br s, H-25), 5.99 (1H, br s, H-2), 5.36 (1H, t, $J = 3.4$ Hz, H-9), 4.78 (1H, m, H-4), 4.69 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 4.14 (1H, br s, –OH), 2.07 (2H, m, H-8), 1.98 and 1.35 (1H, m ea, H-13), 1.94 (2H, m, H-18), 1.88 (1H, m, H-11), 1.79 and 1.48 (1H, m ea, H-5), 1.75 and 1.20 (1H, m ea, H-16), 1.69 (3H, s, Me-21), 1.57 (1H, m, H-14), 1.55 (2H, m, H-12), 1.53 and 1.42 (1H, m ea, H-7), 1.15 (2H, m, H-17), 0.95 (3H, s, Me-24), 0.91 (3H, s, Me-22), 0.81 (3H, d, $J = 7.0$ Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9 (C-1), 117.1 (C-2), 169.9 (C-3), 65.5 (C-4), 44.8 (C-5), 34.4 (C-6), 31.7 (C-7), 22.7 (C-8), 119.6 (C-9), 141.5 (C-10), 42.5 (C-11), 23.1 (C-12), 28.9 (C-13), 38.6 (C-14), 42.9 (C-15), 38.8 (C-16), 22.0 (C-17), 38.5 (C-18), 146.6 (C-19), 109.6 (C-20), 22.5 (C-21), 22.5 (C-22), 15.5 (C-23), 22.5 (C-24), 97.5 (C-25).

5.1.33. Oxidation of 40 with $^1O_2$: 4*S*-acetoxy-25-hydroxy-*ent*-isodysidiola-2,9,19-trien-1,25-olide (3a). Oxidation of **40** (30 mg, 0.073 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 9:1) compound **3a** (30 mg, 93%). Spectroscopic and physical data for the mixture of α and β epimers at C_{20}. $[\alpha]_D^{22}$ −10.4 (*c* 1.01, $CHCl_3$); IR (film, cm^{-1}) 3381, 3075, 2936, 1748, 1651, 1445, 1377, 1227, 1132, 1030, 955, 889; EMIE [*m*/*z* (%)] 444 (M^+, 1), 361 (4), 301 (34), 256 (20), 213 (6), 173 (54), 105 (51); HREIMS calcd for $C_{27}H_{40}O_5$ (M^+) 444.2876, found (M^+) 444.2869. Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (1H, br s, H-25), 5.92 (1H, s, H-2), 5.51 (1H, d, *J* = 9.4 Hz, H-4), 5.36 (1H, t, *J* = 3.7 Hz, H-9), 4.79 (1H, br s, –OH), 4.68 (1H, br s, H_A-20), 4.63 (1H, br s, H_B-20), 2.11 (3H, s, –OOC*Me*), 2.09 and 1.45 (1H, m ea, H-5), 2.04 (2H, m, H-8), 1.95 and 1.34 (1H, m ea, H-13), 1.95 (2H, m, H-18), 1.79 (1H, m, H-11), 1.74 and 1.22 (1H, m ea, H-16), 1.67 (3H, s, Me-21), 1.58 (1H, m, H-14), 1.58 (2H, m, H-12), 1.32 (2H, m, H-7), 1.15 (2H, m, H-17), 0.91 (3H, s, Me-22), 0.90 (3H, s, Me-24), 0.80 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4 (C-1), 117.9 (C-2), 168.2 (C-3), 67.3 (C-4), 42.9 (C-5), 34.6 (C-6), 31.2 (C-7), 22.5 (C-8), 119.4 (C-9), 141.4 (C-10), 42.4 (C-11), 22.6 (C-12), 28.8 (C-13), 38.3 (C-14), 42.9 (C-15), 38.8 (C-16), 22.1 (C-17), 38.5 (C-18), 146.3 (C-19), 109.6 (C-20), 22.5 (C-21), 22.4 (C-22), 15.5 (C-23), 22.4 (C-24), 97.6 (C-25), 171.1 (–O*OC*Me), 20.9 (–OOC*Me*). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, br s, H-25), 5.96 (1H, s, H-2), 5.59 (1H, d, *J* = 9.4 Hz, H-4), 5.36 (1H, t, *J* = 3.7 Hz, H-9), 4.79 (1H, br s, –OH), 4.68 (1H, br s, H_A-20), 4.63 (1H, br s, H_B-20), 2.08 (3H, s, –OOC*Me*), 2.09 and 1.45 (1H, m ea, H-5), 2.04 (2H, m, H-8), 1.95 and 1.34 (1H, m ea, H-13), 1.95 (2H, m, H-18), 1.79 (1H, m, H-11), 1.74 and 1.22 (1H, m ea, H-16), 1.68 (3H, s, Me-21), 1.58 (1H, m, H-14), 1.58 (2H, m, H-12), 1.32 (2H, m, H-7), 1.15 (2H, m, H-17), 0.91 (3H, s, Me-22), 0.88 (3H, s, Me-24), 0.80 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C-1), 118.7 (C-2), 167.5 (C-3), 66.8 (C-4), 42.9 (C-5), 34.6 (C-6), 29.6 (C-7), 22.5 (C-8), 119.4 (C-9), 141.4 (C-10), 42.4 (C-11), 22.6 (C-12), 28.8 (C-13), 38.3 (C-14), 42.9 (C-15), 38.8 (C-16), 22.1 (C-17), 38.5 (C-18), 146.6 (C-19), 109.6 (C-20), 22.5 (C-21), 22.4 (C-22), 15.5 (C-23), 22.4 (C-24), 97.7 (C-25), 170.3 (–O*OC*Me), 20.9 (–OOC*Me*).

5.1.34. Oxidation of 41 with $^1O_2$: 4*R*,25-dihydroxy-*ent*-isodysidiola-2,9,19-trien-1,25-olide (4b). Oxidation of **41** (28 mg, 0.076 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 8:2) compound **4b** (26 mg, 85%). Spectroscopic and physical data for the mixture of α and β epimers at C_{20}. $[\alpha]_D^{22}$ +41.8 (*c* 0.93, $CHCl_3$); IR (film, cm^{-1}) 3401, 3075, 2934, 1755, 1651, 1462, 1379, 1136, 1071, 953, 889; FABMS [*m*/*z* (%)] 403 (M^++ H, 5), 367 (10), 319 (12), 289 (4), 259 (19), 154 (71), 91 (77); HRFABMS calcd for $C_{25}H_{39}O_4$ (M^++H) 403.2848; found (M^++H) 403.2855. Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (1H, br s, H-25), 6.02 (1H, s, H-2), 5.34 (1H, br s, H-9), 5.10 (1H, br s, –OH), 4.78 (1H, d, *J* = 8.7 Hz, H-4), 4.66 (1H, s, H_A-20), 4.60 (1H, s, H_B-20), 2.49 (1H, br s, –OH), 2.10 (2H, m, H-8), 1.96 and 1.34 (1H, m ea, H-13), 1.93 (2H, m, H-18), 1.91 (1H, m, H-11), 1.79 and 1.63 (1H, m ea, H-5), 1.77 and 1.14 (1H, m ea, H-16), 1.66 (3H, s, Me-21), 1.60 and 1.14 (1H, m ea, H-12), 1.55 (1H, m, H-14), 1.54 and 1.23 (1H, m ea, H-7), 1.17 (2H, m, H-17), 1.01 (3H, s, Me-24), 0.90 (3H, s, Me-22), 0.80 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C-1), 116.9 (C-2), 170.8 (C-3), 65.8 (C-4), 45.0 (C-5), 34.3 (C-6), 30.7 (C-7), 22.5 (C-8), 119.2 (C-9), 141.9 (C-10), 42.6 (C-11), 23.3 (C-12), 29.0 (C-13), 38.8 (C-14), 43.1 (C-15), 38.7 (C-16), 22.2 (C-17), 38.5 (C-18), 146.5 (C-19), 109.5 (C-20), 22.4 (C-21), 22.3 (C-22), 15.5 (C-23), 23.4 (C-24), 97.6 (C-25). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (1H, br s, H-25), 5.90 (1H, s, H-2), 5.34 (1H, br s, H-9), 5.10 (1H, br s, –OH), 4.78 (1H, d, *J* = 8.7 Hz, H-4), 4.68 (1H, s, H_A-20), 4.63 (1H, s, H_B-20), 2.49 (1H, br s, –OH), 2.10 (2H, m, H-8), 1.96 and 1.34 (1H, m ea, H-13), 1.93 (2H, m, H-18), 1.91 (1H, m, H-11), 1.79 and 1.63 (1H, m ea, H-5), 1.77 and 1.14 (1H, m ea, H-16), 1.68 (3H, s, Me-21), 1.60 and 1.14 (1H, m ea, H-12), 1.55 (1H, m, H-14), 1.54 and 1.23 (1H, m ea, H-7), 1.17 (2H, m, H-17), 1.00 (3H, s, Me-24), 0.89 (3H, s, Me-22), 0.80 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1 (C-1), 117.3 (C-2), 170.5 (C-3), 65.5 (C-4), 44.6 (C-5), 34.3 (C-6), 29.6 (C-7), 22.6 (C-8), 119.3 (C-9), 141.9 (C-10), 42.6 (C-11), 23.2 (C-12), 29.0 (C-13), 38.8 (C-14), 43.1 (C-15), 38.7 (C-16), 22.2 (C-17), 38.5 (C-18), 146.5 (C-19), 109.5 (C-20), 22.4 (C-21), 22.3 (C-22), 15.5 (C-23), 23.8 (C-24), 97.8 (C-25).

5.1.35. Oxidation of 42 with $^1O_2$: 4*R*-acetoxy-25-hydroxy-*ent*-isodysidiola-2,9,19-trien-1,25-olide (3b). Oxidation of **42** (34 mg, 0.083 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 8:2) compound **3b** (33 mg, 90%). Spectroscopic and physical data for the mixture of α and β epimers at C_{20}. $[\alpha]_D^{22}$ +22.5 (*c* 0.96, $CHCl_3$); mp = 143–144 °C; IR (film, cm^{-1}) 3381, 3077, 2934, 1748, 1651, 1445, 1377, 1229, 1134, 1030, 955, 889; EMIE [*m*/*z* (%)] 444 (M^+, 1), 361 (5), 301 (32), 256 (20), 213 (7), 173 (56), 105 (48); HREIMS calcd for $C_{27}H_{40}O_5$(M^+) 444.2876, found (M^+) 444.2872. Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (1H, br s, H-25), 5.92 (1H, s, H-2), 5.48 (1H, d, *J* = 9.7 Hz, H-4), 5.35 (1H, br s, H-9), 4.68 (1H, br s, H_A-20), 4.60 (1H, br s, H_B-20), 2.12 (3H, s, –OOC*Me*), 2.06 (2H, m, H-8), 1.96 and 1.35 (1H, m ea, H-13), 1.93 (2H, m, H-18), 1.83 (1H, m, H-11), 1.80 and 1.14 (1H, m ea, H-16), 1.79 and 1.67 (1H, m ea, H-5), 1.67 (3H, s, Me-21), 1.57 (1H, m, H-14), 1.46 (2H, m, H-12), 1.33 and 1.24 (1H, m ea, H-7), 1.19 (2H, m, H-17), 0.91 (3H, s, Me-22), 0.90 (3H, s, Me-24), 0.80 (3H, d, *J* = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (C-1), 118.0 (C-2), 168.1 (C-3), 67.3 (C-4), 42.3 (C-5), 34.3 (C-6), 30.4 (C-7), 22.4 (C-8), 119.3 (C-9), 141.7 (C-10), 42.7 (C-11), 23.3 (C-12), 29.0 (C-13), 38.8 (C-14), 43.1 (C-15), 38.7 (C-16), 22.3 (C-17), 38.5 (C-18), 146.3 (C-19), 109.5 (C-20), 22.4 (C-21), 22.3 (C-22), 15.5 (C-23), 22.9 (C-24), 97.5 (C-25), 171.1 (–O*OC*Me), 21.0

(–OOC*Me*). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (1H, br s, H-25), 5.94 (1H, s, H-2), 5.59 (1H, d, J = 8.6 Hz, H-4), 5.35 (1H, br s, H-9), 4.60 (1H, br s, H_A-20), 4.58 (1H, br s, H_B-20), 2.12 (3H, s, –OOC*Me*), 2.06 (2H, m, H-8), 1.96 and 1.35 (1H, m ea, H-13), 1.93 (2H, m, H-18), 1.83 (1H, m, H-11), 1.80 and 1.14 (1H, m ea, H-16), 1.79 and 1.67 (1H, m ea, H-5), 1.67 (3H, s, Me-21), 1.57 (1H, m, H-14), 1.46 (2H, m, H-12), 1.33 and 1.24 (1H, m ea, H-7), 1.19 (2H, m, H-17), 0.91 (3H, s, Me-22), 0.90 (3H, s, Me-24), 0.80 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (C-1), 118.0 (C-2), 168.1 (C-3), 67.3 (C-4), 42.3 (C-5), 34.3 (C-6), 30.4 (C-7), 22.4 (C-8), 119.3 (C-9), 141.7 (C-10), 42.7 (C-11), 23.3 (C-12), 29.0 (C-13), 38.8 (C-14), 43.1 (C-15), 38.7 (C-16), 22.3 (C-17), 38.5 (C-18), 146.3 (C-19), 109.5 (C-20), 22.4 (C-21), 22.3 (C-22), 15.5 (C-23), 22.9 (C-24), 97.5 (C-25), 170.7 (–O*OC*Me), 21.0 (–OOC*Me*).

5.1.36. Reaction of 29 with 3-bromofuran/*n*-BuLi: 1,25-epoxy-4,9-cyclo-*ent*-isodysidiola-1,3(25),10,19-tetraen-4*R*-ol (43). Reaction of **29** (25 mg, 0.083 mmol) with 3-bromofuran/*n*-BuLi (as described before for compounds **36/37**) yields after column chromatography over silica gel (Hex/EtOAc 99:1) compound **43** (28 mg, 91%). $[\alpha]_D^{22}$ + 7.4 (*c* 0.54, $CHCl_3$); IR (film, cm^{-1}) 3472, 3073, 2953, 1462, 1377, 1209, 1165, 1067, 1024, 876, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1H, s, H-25), 7.39 (1H, s, H-1), 6.48 (1H, s, H-2), 4.70 (1H, s, H_A-20), 4.68 (1H, s, H_B-20), 2.71 (1H, t, J = 2.9 Hz, H-9), 2.02 (1H, t, J = 7.0 Hz, H_A-18), 1.98 (1H, t, J = 7.0 Hz, H_B-18), 1.90 (1H, d, J = 14.0 Hz, H_A-5), 1.72 (3H, s, Me-21), 1.52 (1H, d, J = 14.0 Hz, H_A-5), 1.10 (3H, s, Me-24), 2.17–0.98 (13H, m), 0.91 (3H, s, Me-22), 0.81 (3H, d, J = 6.9 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (C-1), 109.5 (C-2), 131.6 (C-3), 72.7 (C-4), 52.2 (C-5), 37.3 (C-6), 33.1 (C-7), 23.4 (C-8), 43.0 (C-9), 139.1 (C-10), 137.9 (C-11), 20.9 (C-12), 26.0 (C-13), 32.3 (C-14), 38.7 (C-15), 39.8 (C-16), 22.3 (C-17), 38.5 (C-18), 146.2 (C-19), 109.6 (C-20), 22.4 (C-21), 21.1 (C-22), 15.0 (C-23), 22.4 (C-24), 139.0 (C-25); EMIE [*m*/*z* (%)] 368 (M^+, 8), 285 (6), 258 (50), 176 (100), 145 (8), 105 (16); HREIMS calcd for $C_{25}H_{36}O_2$(M^+) 368.2715, found (M^+) 368.2718.

5.1.37. Oxidation of 43 with $^1O_2$: 4*R*,25-dihydroxy-4,9-cyclo-2,10,19-*ent*-isodysidiola-2,10,19-trien-1, 25-olide (5). Oxidation of **43** (25 mg, 0.068 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 9:1) compound **5** (23 mg, 85%). Spectroscopic and physical data for the mixture of α and β epimers at C_{20}. $[\alpha]_D^{22}$ − 29.5 (*c* 0.74, $CHCl_3$); IR (film, cm^{-1}) 3360, 3077, 2940, 1753, 1445, 1379, 1130, 1090, 951, 885, 845; EMIE [*m*/*z* (%)] 400 (M^+, 1), 368 (4), 317 (5), 258 (17), 221 (12), 176 (34); HREIMS calcd for $C_{25}H_{36}O_4$(M^+) 400.2614, found (M^+) 400.2609. Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (1H, s, H-25), 6.07 (1H, s, H-2), 4.91 (1H, br s, –OH), 4.70 (2H, s, H-20), 4.08 (1H, br s, –OH), 3.09 (1H, s, H-9), 2.09 (2H, m, H-12), 1.97 (2H, t, J = 7.2 Hz, H-18), 1.89 (1H, m, H-14), 1.83 and 1.46 (1H, m ea, H-17), 1.75 and 1.48 (1H, d, J = 14.4 Hz, H-5), 1.74 and 1.42 (1H, m ea, H-13), 1.71 (3H, s, Me-21), 1.52 (2H, m, H-8), 1.46 (2H, m, H-16), 1.19 and 1.14 (1H, m ea, H-7), 1.12 (3H, s, Me-24), 0.90 (3H, s, Me-22), 0.81 (3H, d, J = 6.8 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C-1), 119.2 (C-2), 170.3 (C-3), 75.5 (C-4), 50.4 (C-5), 37.0 (C-6), 33.0 (C-7), 22.4 (C-8), 40.1 (C-9), 137.4 (C-10), 139.6 (C-11), 21.1 (C-12), 25.9 (C-13), 32.3 (C-14), 38.8 (C-15), 39.7 (C-16), 22.9 (C-17), 38.5 (C-18), 146.1 (C-19), 109.9 (C-20), 22.3 (C-21), 21.2 (C-22), 15.1 (C-23), 22.1 (C-24), 97.9 (C-25). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (1H, s, H-25), 5.94 (1H, s, H-2), 4.91 (1H, br s, –OH), 4.66 (1H, s, H_A-20), 4.65 (1H, s, H_B-20), 4.08 (1H, br s, –OH), 2.79 (1H, s, H-9), 2.09 (2H, m, H-12), 1.97 (2H, t, J = 7.2 Hz, H-18), 1.90 and 1.47 (1H, d, J = 14.4 Hz, H-5), 1.89 (1H, m, H-14), 1.83 and 1.46 (1H, m ea, H-17), 1.74 and 1.42 (1H, m ea, H-13), 1.70 (3H, s, Me-21), 1.52 (2H, m, H-8), 1.46 (2H, m, H-16), 1.19 and 1.14 (1H, m ea, H-7), 1.10 (3H, s, Me-24), 0.89 (3H, s, Me-22), 0.80 (3H, d, J = 6.4 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C-1), 118.4 (C-2), 168.8 (C-3), 75.2 (C-4), 52.3 (C-5), 37.0 (C-6), 32.3 (C-7), 22.1 (C-8), 40.8 (C-9), 138.0 (C-10), 139.2 (C-11), 21.0 (C-12), 25.9 (C-13), 32.2 (C-14), 38.8 (C-15), 39.8 (C-16), 22.9 (C-17), 38.5 (C-18), 145.8 (C-19), 109.8 (C-20), 22.4 (C-21), 21.1 (C-22), 15.1 (C-23), 22.0 (C-24), 98.4 (C-25).

5.1.38. Reaction of 35 with 3-bromofuran/*n*-BuLi: 20-methoxy-1,25-epoxy-21(19 → 18)abeo-4,9-cyclo-*ent*-isodysidiola-1,3(25),10,18*E*-tetraen-4*R*-ol (44). By reaction of **35** (61 mg, 0.18 mmol) with 3-bromofuran/*n*-BuLi (as described before for compounds **36/37**) yields after column chromatography over silica gel (Hex/EtOAc 96:4) compound **44** (58 mg, 79%). $[\alpha]_D^{22}$ + 39.4 (*c* 0.76, $CHCl_3$); IR (film, cm^{-1}) 3445, 2930, 1458, 1379, 1161, 1101, 1074, 1024, 874, 791; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (1H, s, H-25), 7.38 (1H, s, H-1), 6.47 (1H, s, H-2), 5.38 (1H, t, J = 6.8 Hz, H-19), 3.91 (2H, d, J = 6.8 Hz, H-20), 3.32 (3H, s, –O*Me*), 2.70 (1H, t, J = 2.7 Hz, H-9), 1.88 (1H, d, J = 14.0 Hz, H_A-5), 1.69 (3H, s, Me-21), 1.50 (1H, d, J = 14.0 Hz, H_B-5), 1.10 (3H, s, Me-24), 2.18–0.97 (16H, m), 0.92 (3H, s, Me-22), 0.82 (3H, d, J = 6.7 Hz, Me-23); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0 (C-1), 109.5 (C-2), 131.7 (C-3), 72.7 (C-4), 52.1 (C-5), 37.3 (C-6), 33.1 (C-7), 23.4 (C-8), 43.9 (C-9), 138.9 (C-10), 137.8 (C-11), 20.8 (C-12), 25.9 (C-13), 32.2 (C-14), 38.3 (C-15), 38.6 (C-16), 34.0 (C-17), 141.2 (C-18), 120.4 (C-19), 69.0 (C-20), 16.6 (C-21), 21.1 (C-22), 14.9 (C-23), 22.4 (C-24), 139.1 (C-25), 57.8 (–O*Me*); EMIE [*m*/*z* (%)] 398 (M^+, 1), 366 (3), 288 (22), 249 (13), 217 (52), 176 (100), 105 (24); HREIMS calcd for $C_{26}H_{38}O_3$ (M^+) 398.2821, found (M^+) 398.2826.

5.1.39. Oxidation of 44 with $^1O_2$: 20-methoxy-4*R*,25-dihydroxy-21(19 → 18)abeo-4,9-cyclo-*ent*-isodysidiola-2, 10,18*E*-trien-1,25-olide (6). Oxidation of **44** (23 mg, 0.058 mmol) (as described before for compound **2a**) yields after column chromatography over silica gel (Hex/EtOAc 85:15) compound **6** (18 mg, 72%). Spectroscopic and physical data for the mixture of α and β epimers at C_{20}. $[\alpha]_D^{22}$ − 1.2 (*c* 0.33, $CHCl_3$); IR (film, cm^{-1}) 3401, 3075, 2934, 1755, 1651, 1462, 1379, 1136, 1071,

953, 889; FABMS [*m/z* (%)] 416 (M^+−Me, 14), 307 (15), 253 (6), 154 (100), 91 (52). Major component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29–6.25 (1H, m, H-25), 5.79 (1H, s, H-2), 5.50 (1H, t, J = 7.7 Hz, H-19), 4.06–3.86 (2H, m, H-20), 3.45 (3H, s, –O*Me*), 3.07 (1H, br s, H-9), 2.14 (2H, m, H-12), 2.01 (2H, m, H-17), 1.78 (1H, m, H-14), 1.68 (3H, s, Me-21), 1.62 and 1.43 (1H, m ea, H-5), 1.58 (1H, m, H-16), 1.54 (2H, m, H-8), 1.30 (2H, m, H-13), 1.12 (2H, m, H-7), 1.10 (3H, s, Me-24), 0.86 (3H, d, J = 6.7 Hz, Me-23), 0.81 (3H, s, Me-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C-1), 117.7 (C-2), 172.1 (C-3), 75.6 (C-4), 51.5 (C-5), 37.3 (C-6), 33.6 (C-7), 23.5 (C-8), 40.0 (C-9), 138.1 (C-10), 139.0 (C-11), 22.7 (C-12), 27.3 (C-13), 32.8 (C-14), 40.1 (C-15), 40.0 (C-16), 33.2 (C-17), 143.3 (C-18), 118.4 (C-19), 69.5 (C-20), 17.2 (C-21), 22.3 (C-22), 15.8 (C-23), 22.4 (C-24), 98.3 (C-25), 58.6 (–O*Me*). Minor component: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60–6.54 (1H, m, H-25), 6.01 (1H, s, H-2), 5.50 (1H, t, J = 7.7 Hz, H-19), 4.06-3.86 (2H, m, H-20), 3.39 (3H, s, –O*Me*), 2.74 (1H, br s, H-9), 2.14 (2H, m, H-12), 2.01 (2H, m, H-17), 1.78 (1H, m, H-14), 1.68 (3H, s, Me-21), 1.62 and 1.43 (1H, m ea, H-5), 1.58 (1H, m, H-16), 1.54 (2H, m, H-8), 1.30 (2H, m, H-13), 1.12 (2H, m, H-7), 1.10 (3H, s, Me-24), 0.86 (3H, d, J = 6.7 Hz, Me-23), 0.81 (3H, s, Me-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C-1), 118.2 (C-2), 172.1 (C-3), 75.8 (C-4), 51.4 (C-5), 37.3 (C-6), 33.6 (C-7), 23.5 (C-8), 40.7 (C-9), 138.1 (C-10), 139.0 (C-11), 22.7 (C-12), 27.3 (C-13), 32.8 (C-14), 39.4 (C-15), 40.0 (C-16), 33.2 (C-17), 142.7 (C-18), 118.4 (C-19), 69.5 (C-20), 17.3 (C-21), 22.3 (C-22), 15.8 (C-23), 22.4 (C-24), 97.3 (C-25), 58.2 (–O*Me*).

5.1.40. Oxidation of 39/41 with TPAP: 25-epoxy-*ent*-isodysidiola-1,3(25),9,19-tetraen-4-one (46). Oxidation of **39/41** (67 mg, 0.18 mmol) (as described before for compound **20**) yields after column chromatography over silica gel (Hex/EtOAc 99:1) compound **45** (62 mg, 93%). $[\alpha]_D^{22}$ + 48.6 (*c* 1.02, $CHCl_3$); IR (film, cm^{-1}) 3133, 3073, 2934, 1672, 1562, 1510, 1454, 1379, 1155, 1051, 874; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (1H, dd, J = 1.8 and 0.8 Hz, H-25), 7.39 (1H, t, J = 1.8 Hz, H-1), 6.72 (1H, dd, J = 1.8 and 0.8 Hz, H-2), 5.33 (1H, t, J = 3.6 Hz, H-9), 4.69-4.57 (2H, m, H-20), 2.73 (1H, d, J = 14.8 Hz, H_A-5), 2.57 (1H, d, J = 14.8 Hz, H_B-5), 1.67 (3H, s, Me-21), 2.14–1.02 (16H, m), 0.99 (3H, s, Me-22), 0.89 (3H, s, Me-24), 0.79 (3H, d, J = 7.0 Hz, Me-23); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.0 (C-1), 108.9 (C-2), 129.9 (C-3), 195.5 (C-4), 48.6 (C-5), 35.6 (C-6), 30.9 (C-7), 23.1 (C-8), 119.8 (C-9), 142.0 (C-10), 42.4 (C-11), 23.6 (C-12), 29.3 (C-13), 39.3 (C-14), 43.4 (C-15), 39.0 (C-16), 22.6 (C-17), 38.8 (C-18), 146.6 (C-19), 109.8 (C-20), 22.6 (C-21), 22.6 (C-22), 15.8 (C-23), 23.8 (C-24), 147.2 (C-25); EMIE [*m/z* (%)] 368 (M^+, 6), 285 (5), 258 (38), 217 (39), 176 (100), 149 (23), 105 (43); HREIMS calcd for $C_{25}H_{36}O_2$ (M^+) 368.2715, found (M^+) 368.2705.

5.1.41. Reaction of 45 with *p*-TsOH/acetone: 1,25-epoxy-*ent*-isodysidiola-1,3(25),9,18-tetraen-4-one (46). To a solution of **45** (35 mg, 0.095 mmol) in acetone (1 mL), *p*-TsOH (18 mg, 0.095 mmol) was added. The reaction mixture was heated to 55 °C for 24 h. The reaction mixture was diluted with water and extracted with Et_2O. The extracts were washed with 6%, aqueous $NaHCO_3$ solution and brine. Evaporation of the solvent followed by chromatography over silica gel (Hex/EtOAc 98:2) yielded **46** (26 mg, 74%). $[\alpha]_D^{22}$ + 36.1 (*c* 0.92, $CHCl_3$); IR (film, cm^{-1}) 3133, 3050, 2928, 1672, 1562, 1510, 1452, 1379, 1155, 1051, 874; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (1H, dd, J = 1.8 and 0.8 Hz, H-25), 7.40 (1H, t, J = 1.8 Hz, H-1), 6.74 (1H, dd, J = 1.8 and 0.8 Hz, H-2), 5.37 (1H, t, J = 3.6 Hz, H-9), 5.10 (1H, t, J = 5.8 Hz, H-18), 2.74 (1H, d, J = 14.4 Hz, H_A-5), 2.60 (1H, d, J = 14.4 Hz, H_B-5), 1.68 and 1.57 (3H, s ea, Me-20 and Me-21), 2.14-1.00 (14H, m), 0.99 (3H, s, Me-22), 0.93 (3H, s, Me-23), 0.81 (3H, d, J = 7.0 Hz, Me-24); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.3 (C-1), 109.0 (C-2), 130.1 (C-3), 195.5 (C-4), 48.9 (C-5), 35.8 (C-6), 30.9 (C-7), 23.1 (C-8), 120.0 (C-9), 141.7 (C-10), 42.6 (C-11), 23.5 (C-12), 29.2 (C-13), 39.1 (C-14), 43.4 (C-15), 39.4 (C-16), 23.1 (C-17), 125.6 (C-18), 131.0 (C-19), 17.8 (C-20), 25.9 (C-21), 22.5 (C-22), 15.8 (C-23), 23.6 (C-24), 147.2 (C-25); EMIE [*m/z* (%)] 368 (M^+, 2), 329 (5), 258 (7), 213 (5), 176 (100), 105 (17), 69 (34); HREIMS calcd for $C_{25}H_{36}O_2$(M^+) 368.2715, found (M^+) 368.2709.

5.2. Inhibition of tumour cell growth assay

The in vitro antitumour activity for compounds **1b**, **2a**, **2b**, **3a**, **3b**, **4a**, **4b**, **5**, **6**, **36/37**, **39/41**, **45** and **46** was determined by measurement of its cytostatic and cytotoxic properties in human tumour cell lines by the XTT assay, in which the metabolic activity of viable cells was assessed. Cells were incubated in RPMI-1640 (HL-60) or DMEM (HeLa, A549, HT-29) culture medium containing 10% foetal calf serum, in the absence and presence of the indicated compound at a concentration range of 10^{-4} to 10^{-8} M in 96-well plates, and following 72-h incubation at 37 °C in a humidified atmosphere of air/CO_2 (19:1) the XTT assay was performed. Measurements were done in triplicate, and the IC_{50} value, defined as the drug concentration required to cause 50% inhibition in the cellular proliferation with respect to untreated controls, was determined. Values shown are means ± SE of three independent determinations.[35]

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