Tetrahedron 64 (2008) 5502–5508

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A stereoselective route towards heliannuol A

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ARTICLE INFO

Article history:
Received 24 February 2008
Received in revised form 26 March 2008
Accepted 29 March 2008
Available online 3 April 2008

ABSTRACT

Both epimers of Heliannuol A, first heliannane reported in the literature, isolated from *Heliannthus annuus*, have been prepared individually in a stereoselective route using a ring closing metathesis (RCM) as a key step to obtain the eight-membered ring. Very good overall yield was obtained in both cases.

1. Introduction

Heliannuol A is the first heliannane reported in the literature.[1] It was isolated from sunflower leaves and all the following members of the family have been isolated from the same source, but in different sunflower varieties. Surprisingly, no heliannuols have been isolated from other terrestrial sources so far. However, the basic heliannane skeleton has been isolated lately from a marine organism, the Indo-Pacific sponge *Haliclona fascigera* (Fig. 1).[2]

Later, the remaining members that conform to the family of the heliannanes have been isolated and they are grouped in function of their structure in four types of skeletons, 7,11-heliannanes; 7,10-heliannanes; 8,10-heliannanes and 8,11-heliannanes (Fig. 2).

2. Results and discussion

There are some previous reports showing the formation of heliannuol A[3] while base catalyzed cyclization towards heliannuol D takes place[4] that will be in good accordance with the biogenetic hypothesis proposed by Macias et al.[1b] However, we have not been able to detect such a process either in the synthesis of the 7,10-heliannane skeleton, or in the synthesis of (±)-heliannuol D.[5] Moreover, several trials to get access to acid-catalyzed cyclization conditions of Heliannuols did not give satisfactory result. This situation prompted us to look for an alternative synthetic methodology that will give us access to the desired 7,11-heliannuol backbone that is shown in the retrosynthetic analysis depicted in Figure 3.

The synthetic procedure presents as key steps the incorporation of the two side chains into the aromatic core of the molecule, the intramolecular cyclization using a ruthenium-catalyzed RCM, and the stereoselective epoxidation of the double bond in the oxepane ring. This synthetic strategy also allowed us to obtain several derivatives of the 7,11-heliannanes.

Starting from a previously synthesized **1** by us in the preparation of (±)-heliannuol D[5] (**1**) (Scheme 1), selective deprotection of the benzyl group at C-2 in the aromatic ring was achieved using $MgBr_2$ in toluene, yielding **2** (78%) as major reaction product and **3**

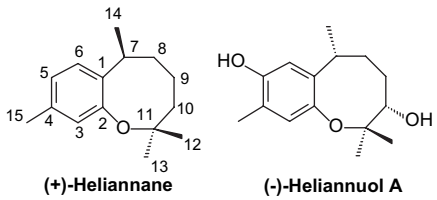

Figure 1. Heliannuol A and heliannane structure.

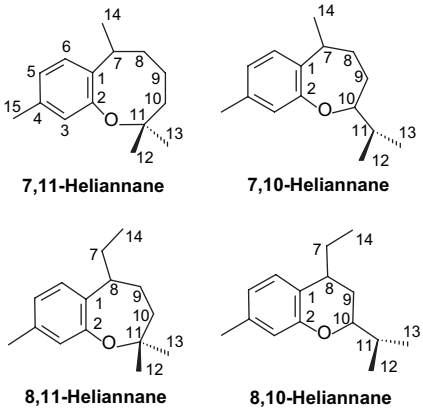

Figure 2. Heliannane skeleton types.

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0040-4020/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tet.2008.03.105

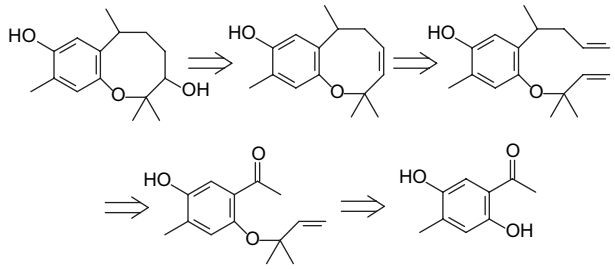
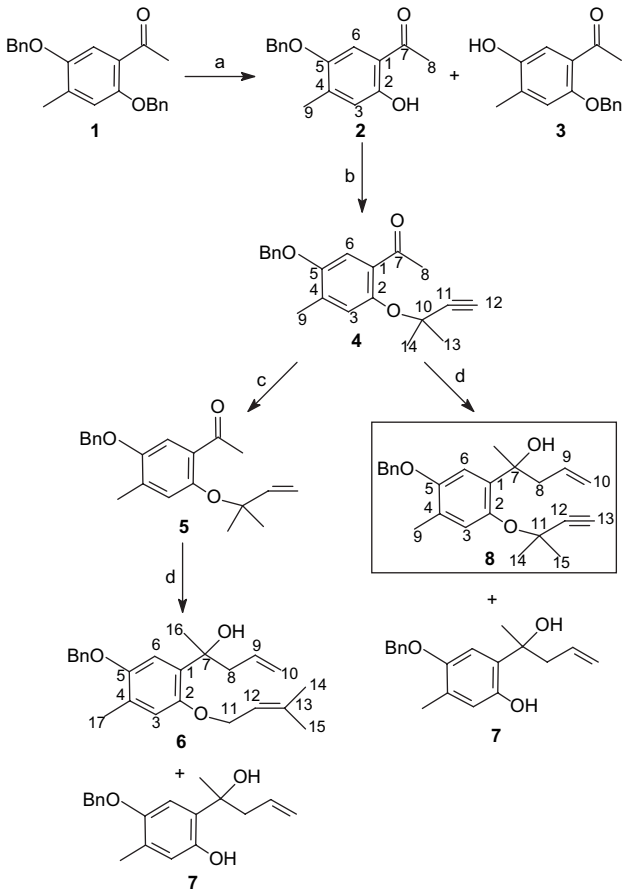


Figure 3. Retrosynthetic analysis.



Scheme 1. Reagents and conditions: (a) $MgBr_2$, toluene (**2** 78%, **3** 15%, 12 h, rt then 1 h, 110 °C); (b) 3-chloro-3-methyl-1-butyne, $CuCl_2$, DBU (95%, 5 h, 0 °C); (c) $Pd(CO_3Ca/Pb)$ (40% w/w), quinoline (60% w/w), H_2, hexane (**5** 92%, 1 h, rt); (d) allyl bromide, Mg, I_2, dry THF (**6** 17%, **7** 35% and **8** 83%, **7** 3%, 10 min, rt).

(15%) as side product. The use of $MgBr_2$ allows selective deprotection when a carbonyl group is close to the benzyl derivative through formation of a chelate between the carbonyl group, the oxygen of the ether, and the magnesium atom.[6] Differentiation between both structures came from the X-ray analysis of the major compound **2**, which confirmed the expected structure (Fig. 4).

Treatment of **2** with 3-chloro-3-methyl-1-butyne under basic conditions (DBU) using $CuCl_2$ as catalyst gave **4** with a 95% yield. Due to the reactive nature of the alkyne protons, several condensation products of unknown nature in the side chain appear when the catalyst is not present.[7]

Previous to the incorporation of the second side chain in the carbonyl group through a Grignard reaction it was necessary to achieve the reduction of the triple bond to avoid possible interferences of the acidic alkynyl proton. In this case, the method consisted on the use of the Lindlar catalyst in the presence of

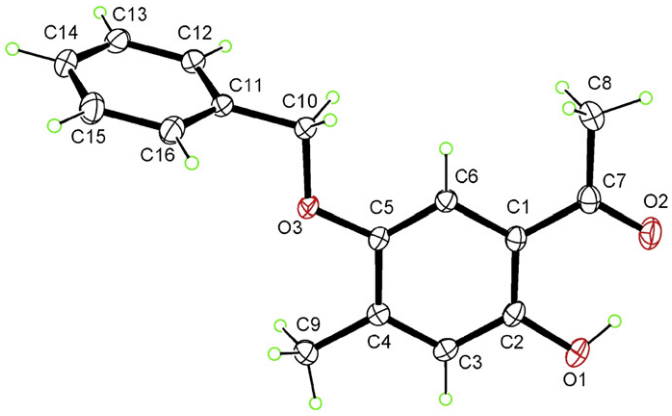


Figure 4. ORTEP diagram of **2**.

quinoline in order to avoid overreductions. After 1 h of reaction a single compound (**5**) with a slightly higher R_f value could be isolated with a 92% yield.

Treatment of compound **5** with allyl bromide and metallic magnesium in dry THF (10 min, rt) led to the formation of two undesired compounds of higher polarity (**6** and **7**). In order to avoid these undesired results, the order of the reactions was changed. Compound **6** obtained could be explained via 1,1-dimethyallyl bromide formation and subsequent S_N2' reaction. Consequently, using **4** as starting material, the incorporation of the side chain in the carbonyl system was achieved through a Grignard reaction, as previously described. After 15 min of reaction two compounds of higher polarity were formed (**8** and **7**).

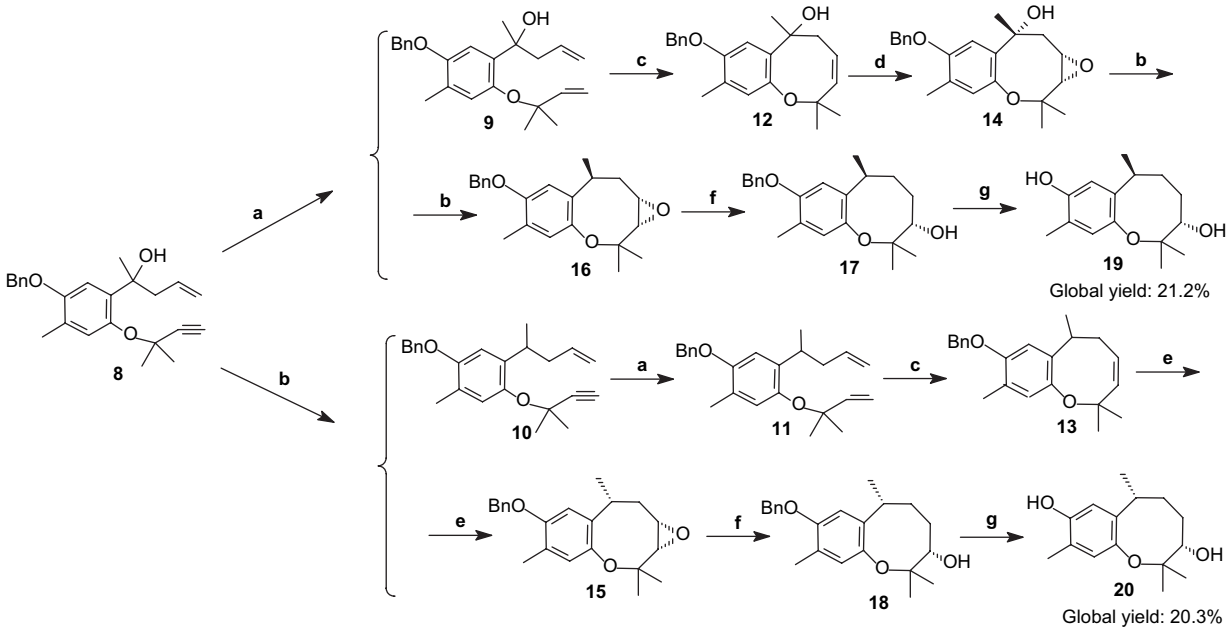
Once the preparation of both side chains is completed, the route takes two different paths, depending on the order that we perform the reactions, but both with the same target, achieving the eight-membered ring (Scheme 2).

If we first perform the reduction of compound **8** under the same conditions as for compound **4**, we obtain the desired compound **9** almost quantitatively, starting material of the reaction of metathesis. From another point of view, heliannuol A does not have hydroxyl group at C-7 in the oxepane ring. Consequently, the hydroxyl group present in compound **8** should be removed prior to or after the metathesis cyclization. Using this sequence of reactions, treatment of **8** with $BF_3{\cdot}Et_2O$ and Et_3SiH (1:0.5:1) at −78 °C yields compound **10** (82%) where the hydroxyl group was removed. Reduction of the triple bond in **10** under the same conditions mentioned for **8** yields the desired compound **11** in a 92%.

The RCM is a synthetic tool that has experienced an extensive use in the synthesis of natural products containing medium to large cycles and has been previously used in several heliannane synthesis.[10] We have used this reaction to get access effectively to the oxepane ring using the second generation Grubbs' catalyst[7] and the two olefins **9** and **11**.

Treatment of the diolefin **9** (0.01 M), carrying a hydroxyl group at C-7 position, with a 10 mol % of the Grubbs' catalyst[8] in degassed DCM over 1 h gave a more polar compound (**12**) in a yield of 90%. When compound **11** was treated under the same conditions, a compound with a higher polarity (**13**) than **11** was obtained in 91% yield.

Direct epoxidation of the 7,11-heliannanes with MCPBA results in no reaction, probably due to the high steric hindrance caused by the two methyl groups and the conformation of the molecule. Looking for small size epoxidizing agents, we selected dioxirane reagents as a feasible reactant. Their use has been demonstrated to be more effective if generated in situ from potassium peroxomonosulphate and ketones, and specially from methyl(trifluoromethyl)dioxirane buffered with potassium bicarbonate.[9]



Scheme 2. Reagents and conditions: (a) Pd(CO_3Ca/Pb) (40% w/w), quinoline (60% w/w), H_2, hexane (**9** 95%, **11** 92%, 1 h, rt); (b) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (**10** 82%, **16** 68%, 10 min at −78 °C and then 1 h, −50 °C); (c) Grubbs' catalyst (10% w/w), CH_2Cl_2 degassed (**12** 90%, **13** 91%); (d) methyl trifluoromethyl ketone, $NaHCO_3$, OXONE®, CH_3CN/Na_2EDTA (82%, 2 h, −2 °C); (e) methyl trifluoromethyl ketone, $NaHCO_3$, OXONE®, Acetone/Na_2EDTA (72%, 2 h, −2 °C); (f) $LiAlH_4$, dry THF (**17** 71%, **18** 75%, 2 h, rt); (g) Pd/C (50% w/w), H_2, CH_2Cl_2 (**19** 98%, **20** 99%).

Usually, a biphasic solvent system DCM/H_2O or Et_2O/H_2O is adopted, but last reports refer CH_3CN/H_2O as the most effective solvent system.[10]

Reaction of compound **12** with methyl trifluoromethyl ketone and OXONE® (potassium peroxomonosulfate, ALDRICH) in CH_3CN/H_2O with $NaHCO_3$ and Na_2EDTA gave only one product of higher polarity in an 82% yield, product **14**. Similar treatment of **13** under the same conditions gave compound **15**. However, the yield in this case was lower (37%). The low polarity of the starting material **13** could be probably the reason for such a low yield due to low solubility in the biphasic acetonitrile/water solvent system. Best results were obtained with an acetone/water solvent system (72%). The diastereoselectivity of this reaction is also remarkable as a racemic diastereoisomer is obtained from each racemic substrate, thus concluding that epoxidation is produced only by one of the two faces of each diastereoisomer. The positive NOE effects observed between the methyl group H-14 and the oxirane protons H-9 and H-10 in **14**, and between H-7 and the oxirane protons in **15** clearly demonstrate that there is an asymmetric induction effect caused by the hydroxyl group at C-7. When the hydroxyl group is present (compound **14**), a relative cis disposition between the hydroxyl group and the epoxide ring occurs. However, when the hydroxyl group is not present (compound **15**) a relative *syn* disposition is obtained between the methyl group and the oxirane ring (Fig. 5).

Next step towards the synthesis of (±)-heliannuol A was to remove the hydroxyl group of compound **14**, prior to the epoxide ring opening. This was achieved using a similar methodology to that used for compound **10**. Thus, treatment of **14** with Et_3SiH (1:1) and $BF_3{\cdot}Et_3O$ (1:0.5) at −78 °C gave **16** in a 68% yield. Epoxide ring opening was achieved in both cases (compounds **15** and **16**) using $LiAlH_4$ in good yields, and finally, Pd/C catalyzed hydrogenation of compounds **17** and **18** gave the corresponding debenzylated compounds **19** and **20** almost quantitatively.

The exact match of chemical shifts and coupling constants for all proton/carbon resonances between **20** and (+)-heliannuol A

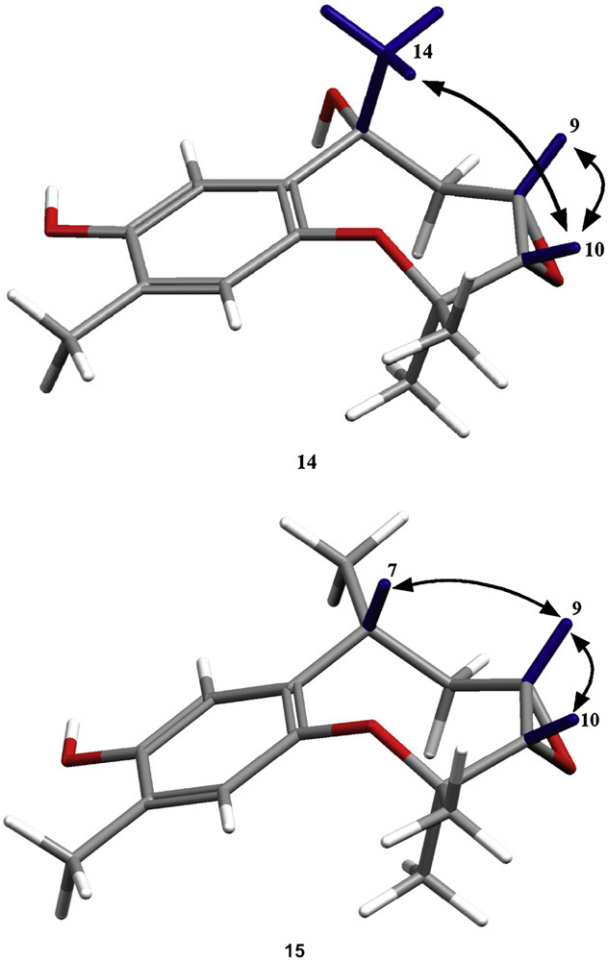


Figure 5. NOE in **14** and **15**.

isolated from *Helianthus annuus* allowed to identify this synthetic product as the natural epimer.[1]

3. Conclusion

In summary, it can be concluded that the synthesis of compounds **19** and **20** can be selectively achieved in 11 steps by changing the order of the deoxygenation and Lindlar reduction reactions. Using the benzylated hydroquinone **1** as starting material, the overall yield for (±)-*epi*-heliannuol A (**19**) and for (±)-heliannuol A (**20**) is 21.2 and 20.3%, respectively.

4. Experimental

4.1. General

Commercially available chemicals were used as received. Dry THF was obtained by distillation from sodium benzophenone ketyl. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on both Varian Unity Spectrometers with a sample temperature of 25 °C using $CDCl_3$ as solvent and TMS as internal reference. Mass spectroscopy was carried out using a GC–MS VG1250 apparatus (ion trap detector) in EI mode. FTIR spectra were recorded on a Perkin Elmer Spectrum BX spectrometer and UV–vis spectra were obtained with a Varian Cary BIO 50 spectrometer. Mps of crystalline compounds were determined on a Büchi Melting Point B-545 apparatus and are uncorrected. Purities of synthesized compounds were determined by NMR and HPLC methods, and corroborated by HRMS and elemental analysis when appropriate. The diffraction data were collected to θ_{max}=32.6° at T=105 K on a KappaCCD diffractometer equipped with Mo Kα radiation and an Oxford Cryosteam sample chiller.

4.2. Synthetic procedure

*4.2.1. 5-Benzyloxy-2-hydroxy-4-methylacetophenone (**2**)*

To a solution of **1** (2 g, 5.77 mmol) in dry toluene, $MgBr_2$ (1.29 g, 7 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and, then, refluxed for 1 h. Finally, the mixture was neutralized with diluted HCl aq and extracted (5×) with ethyl acetate. The organic layers were combined, the solvent removed under reduced pressure and chromatographed in silica gel CC using hexane/AcOEt (19:1) as eluent. This procedure afforded compounds **2** (78%) and **3** (15%).

*4.2.1.1. Compound **2**.* IR (neat, KBr) ν_{max} 3014, 2932, 2845, 1671 cm^{-1}; UV (MeOH) λ_{max} 235, 260, 349 nm; EIMS *m*/*z* (rel int.) 256 [M]$^+$ (100), 165 [M−C_7H_7]$^+$ (80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (5H, m, H-3′-H-7′), 7.01 (1H, s, H-6), 6.79 (1H, s, H-3), 5.04 (2H, s, H-1′), 2.53 (3H, s, H-8), 2.29 (3H, s, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.3 (C-7), 157.1 (C-2), 149.2 (C-5), 138.9 (C-4), 136.9 (C-6), 128.5 (C-3′, C-7′), 127.9 (C-5′), 127.2 (C-4′, C-6′), 120.1 (C-1), 116.9 (C-2′), 111.8 (C-3), 70.8 (C-1′), 26.5 (C-8), 17.0 (C-9). HREIMS (M$^+$) found 256.1104. $C_{16}H_{16}O_3$ requires 256.1099. Mp 60–63 °C.

*4.2.1.2. Compound **3**.* IR (neat, KBr) ν_{max} 3015, 2934, 2835, 1669 cm^{-1}; UV (MeOH) λ_{max} 236, 260, 350 nm; EIMS *m*/*z* (rel int.) 256 [M]$^+$ (100), 165 [M−C_7H_7]$^+$ (80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (5H, m, H-3′-H-7′), 7.08 (2H, s, H-6, H-3), 5.04 (2H, s, H-1′), 2.56 (3H, s, H-8), 2.25 (3H, s, H-9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2 (C-7), 155.6 (C-2), 150.0 (C-5), 136.8 (C-4), 128.7 (C-6), 128.6 (C-7′, C-3′), 128.0 (C-5′), 127.5 (C-6′,C-4′), 126.1 (C-1), 116.9 (C-2′), 112.2 (C-3), 70.9 (C-1′), 26.8 (C-8), 15.6 (C-9). HREIMS (M$^+$) found 256.1103. $C_{16}H_{16}O_3$ requires 256.1099.

*4.2.2. 5-Benzyloxy-2-(1,1-dimethylprop-1-yn-1-yl)oxy-4-methylacetophenone (**4**)*

To a solution of **2** (1.5 g, 6.2 mmol) in CH_3CN (10 mL) under Ar and cooled in an ice–salt bath (−4 °C) were added DBU (3.7 mL, 25 mmol), $CuCl_2\cdot 2H_2O$ (3 mg, 0.3 mol%) and 1,1-dimethylpropargyl chloride (3.81 g, 37.2 mmol). The resulting solution was allowed to stir at 0 °C for 5 h. Then, the mixture was concentrated at reduced pressure and the residue chromatographed in silica gel CC using hexane/AcOEt (19:1) as eluent, yielding compound **4** (95%).

*4.2.2.1. Compound **4**.* IR (neat, KBr) ν_{max} 3285, 2987, 2834, 1671 cm^{-1}; UV (MeOH) λ_{max} 205, 235, 250 nm; EIMS *m*/*z* (rel int.) 322 [M]$^+$ (16), 255 [M−C_5H_7]$^+$ (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (5H, m, H-3′-H-7′), 7.34 (2H, s, H-6, H-3), 5.02 (2H, s, H-1′), 2.71 (3H, s, H-8), 2.67 (1H, s, H-12), 2.38 (3H, s, H-9), 1.75 (6H, s, H-13, H-14). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0 (C-7), 152.4 (C-2), 148.5 (C-5), 137.1 (C-2′), 132.5 (C-4), 131.0 (C-1), 128.4 (C-4′, C-7′), 127.7 (C-5′), 127.2 (C-3′,C-6′), 124.0 (C-3), 111.5 (C-6), 85.5 (C-11), 74.9 (C-12), 73.8 (C-1′), 70.1 (C-10), 31.6 (C-8), 29.6 (C-13,C-14), 16.7 (C-9). HREIMS (M$^+$) found 322.1559. $C_{21}H_{22}O_3$ requires 322.1569. Mp 36–39 °C.

*4.2.3. Lindlar reduction: preparation of 5-benzyloxy-2-(1,1-dimethylprop-2-en-1-yl)oxy-4-methylacetophenone (**5**), 5-benzyloxy-2-(1,1-dimethylprop-2-en-1-yl)oxy-4-methyl-1-(1-methyl-1-hydroxybut-3-en-1-yl)benzene (**9**), and 5-benzyloxy-2-(1,1-dimethylprop-2-en-1-yl)oxy-4-methyl-1-(1-methylbut-3-en-1-yl)benzene (**11**)*

Quinoline (120 μL) and alkyne (500 mg) were dissolved in hexane (50 mL). Commercially available Lindlar catalyst (200 mg) was added and the resulting suspension was stirred till complete conversion under an atmosphere of H_2 (1 atm). The catalyst was filtered off through a pad of Celite, the solvent was evaporated and the residue was purified by CC (hexane/AcOEt, from 19:1 to 4:1) affording dienes **5** (92%), **9** (95%) and **11** (92%), respectively.

*4.2.3.1. Compound **5**.* IR (neat, KBr) ν_{max} 2985, 2954, 1668 cm^{-1}; UV (MeOH) λ_{max} 215, 235, 295 nm; EIMS *m*/*z* (rel int.) 324 [M]$^+$ (16), 257 [M−C_5H_7]$^+$ (100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (5H, m, H-3′-H-7′), 7.21 (1H, s, H-6), 6.92 (1H, s, H-3), 6.13 (1H, dd, *J*=11 and 17.6, H-11), 5.19 (1H, dd, *J*=0.8 and 17.6, H-12b), 5.17 (1H, dd, *J*=0.8 and 11, H-12a), 5.02 (2H, s, H-7′), 2.61 (3H, s, H-8), 2.22 (3H, s, H-9), 1.47 (6H, s, H-14 and H-15). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4 (C-7), 151.6 (C-2), 149.5 (C-5), 144.0 (C-11), 137.2 (C-2′), 132.4 (C-4), 130.4 (C-1), 128.4 (C-4′, C-6′), 127.7 (C-3′, C-7′), 127.2 (C-5′), 123.2 (C-3), 113.8 (C-12), 111.5 (C-6), 80.9 (C-10), 73.8 (C-1′), 32.0 (C-8), 27.2 (C-13,-14), 16.8 (C-9). HREIMS (M$^+$) found 324.1557. $C_{21}H_{24}O_3$ requires 324.1676.

*4.2.3.2. Compound **9**.* IR (neat, KBr) ν_{max} 2985, 2934, 1648 cm^{-1}; UV (MeOH) λ_{max} 215, 235, 295 nm; EIMS *m*/*z* (rel int.) 366 [M]$^+$ (35), 348 [M−H_2O]$^+$ (85), 257 [M−H_2O−C_7H_7]$^+$ (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M$^+$) found 366.2208. $C_{24}H_{30}O_3$ requires 366.2150.

*4.2.3.3. Compound **11**.* IR (neat, KBr) ν_{max} 3065, 2957, 2944, 1658 cm^{-1}; UV (MeOH) λ_{max} 209, 230, 285 nm; EIMS *m*/*z* (rel int.) 350 [M]$^+$ (10), 382 [M−C_5H_7]$^+$ (55), 241 [M−C_3H_5−C_5H_7]$^+$ (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M$^+$) found 350.2292. $C_{24}H_{30}O_2$ requires 350.2246.

*4.2.4. Grignard reaction: preparation of 5-benzyloxy-4-methyl-2-(3-methylbut-2-en-1-yl)oxy-1-(1-methyl-1-hydroxybut-3-en-1-yl)benzene (**6**), 5-benzyloxy-4-methyl-1-(1-methyl-1-hydroxybut-3-en-1-yl)-2-hydroxybencene (**7**), and 5-benzyloxy-*

Table 1
^{1}H NMR data for compounds **6**, **8**–**19** (400 MHz in $CDCl_3$, signal of residual $CHCl_3$ centred at δ 7.25 ppm)

	6	8	9	10	11	12	13	14	15	16	17	18	19
3	6.80 s	6.80 s	6.80 s	6.68 s	6.67 s	6.73 s	6.56 s	6.78 s	6.60 s	6.65 s	6.66 s	6.65 s	6.52 s
6	6.80 s	7.25 s	6.93 s	7.21 s	6.82 s	7.22 s	6.71 s	7.23 s	6.77 s	6.68 s	6.70 s	6.74 s	6.69 s
7				3.23 ddq	3.23 ddq		2.91 m		2.93 ddq	3.23 ddq	3.19 ddq	3.19 ddq	3.08 ddq
8	2.77 dd	6.88 dd	2.77 dd	2.32 m	2.32 m	3.82 ddd	3.30 m	2.67 dd	2.29 dd	2.50 ddd	2.04 m		2.06 m
	2.48 dd	6.80 dd	2.58 dd			2.24 ddd	2.15 m	2.42 dd	2.25 dd				
9	5.70 dddd	5.52 dddd	5.60 dddd	5.71 dddd	5.71 dddd	5.73 ddd	5.67 ddd	3.31 ddd	3.03 ddd	3.13 ddd	2.05 m		2.05 m
													1.91 dddd
10	5.17 dd	5.06 dd	5.05 dd	4.97 dd	4.92 dd	5.41 dd	5.41 dd	2.59 d	2.52 d	2.68 d	3.43 d	3.65 br d	3.38 d
	5.14 dd	5.00 dd		4.94 dd	4.89 dd								
11	3.35 d		5.01 dd										
12	5.10 ddd		6.18 dd		6.12 dd	1.58[a] s	1.57[a] s	1.44[a] s	1.53[a] s	1.52[a] s	1.44[a] s	1.44[a] s	1.40[a] s
13		2.64 s	5.25 dd	2.50 s	5.19 dd	1.45[a] s	1.37[a] s	1.40[a] s	1.41[a] s	1.41[a] s	1.39[a] s	1.38[a] s	1.35[a] s
			5.21 dd		5.10 dd								
14	1.58[a] s	1.73[a] s	1.58[a] s	1.64 s	1.40 s	1.37 s	1.26 d	1.56 s	1.17 d	1.30 d	1.25 d	1.25 d	1.15 d
15	1.52[a] s	1.72 s	1.52[a] s	1.62 s	1.40 s	2.22 s	2.19 s	2.23 s	2.18 s	2.20 s	2.22 s	2.22 s	2.14 s
16	1.47 s	1.44 s	1.47 s	1.15 d	1.12 d								
17	2.17 s	2.22 s	2.17 s	2.19 s	2.17 s								
1′	5.02 s	5.02 s	5.02 s	5.02 s	5.02 s	5.06 s	5.01 s	5.06 s	5.04 s	5.02 s	5.05 s	5.03 s	
3′–7′	7.36 m	7.36 m	7.36 m	7.36 m	7.36 m	7.40 m	7.40 m	7.40 m	7.35 m	7.36 m	7.35 m	7.35 m	

J (Hz): (**6**) 9,10a=18; 9,10b=10.2; 9,8a=9,8b=7.3; 8a,8b=13.6; 11a,12=11b,12=6.2; 12,13=1.3; 10a,10b=0.9; 12,13a=10.7; 12,13b=17.9; 13a,13b=0.54. (**8**) 9,10a=17.1; 9,10b=10; 9,8a=9,8b=6.5; 8a,8b=13.6; 10a,10b=0.9. (**9**) 9,10a=18; 9,10b=10.2; 9,8a=9,8b=7.3; 8a,8b=13.6; 10a,10b=0.9; 12,13a=10.7; 12,13b=17.9; 13a,13b=0.54. (**10**) 9,10a=17.2; 9,10b=10.3; 9,8a=9,8b=7.3; 7,14=7,8a=7,8b=6.6, 10a,10b=0.8. (**11**) 9,10a=17.3; 9,10b=10.3; 9,8a=9,8b=7.3; 7,14=7,8a=7,8b=7.1, 10a,10b=1.0; 12,13a=10.9; 12,13b=17.6; 13a,13b=0.98. (**12**) 8a,10=1.2; 8a,9=10; 8a,8b=12.8; 9,10=10.7. (**13**) 7,14=6.9; 9,10=10.6. (**14**) 8a,9=3.9; 8a,8b=13.6; 8b,9=11; 9,10=3.9. (**15**) 8a,8b=6.9; 8a,9=8b,9=3.9; 7,14=6.9; 9,10=4.2. (**16**) 9,10=4.2; 9,8a=4.2; 9,8b=8.7; 7,14=7,8a=7,8b=7.4. (**17**) 7,8a=7.5; 7,8b=15.6; 7,14=6.9; 9a,10=9.1. (**18**) 7,14=6.9; 10,9a=7. (**19**) 7,8a=7.4; 7,8b=14.8; 7,14=7.2; 9b,10=9.1; 9b,9a=13.8; 9b,8a=9b,8b=3.1.

[a] Signals may be interchanged.

*4-methyl-2-(1,1-dimethylprop-2-yn-1-yl)oxy-1-(1-methyl-1-hydroxybut-3-en-1-yl)benzene (**8**)*

A catalytic amount of I_2 was added to 23 mg (924 μmol) of magnesium in 1 mL of dry THF in Ar atmosphere at room temperature. The mixture was stirred and 0.5 mL of a solution of **5** (100 mg, 308 μmol) and allyl bromide (77 μL, 924 μmol) in THF (5 mL) was added. The reaction mixture colour changes from orange to colourless. When the colour turns to grey, the remaining solution of **5** and allyl bromide was added and stirred for 10–30 min till a polar compound was observed in TLC. NH_4Cl saturated solution (50 mL) in water was added and the mixture extracted with EtOAc (5×). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated. The mixture was chromatographed (hexane/AcOEt 9:1), yielding compounds **6** (17%) and **7** (35%).

The treatment of **4** (100 mg, 310 μmol) with magnesium (22.3 mg, 930 μmol) and allyl bromide (78 μL, 930 μmol) in THF (5 mL) afforded **8** (83%) and **7** (3%).

*4.2.4.1. Compound **6**.* IR (neat, KBr) ν_{max} 3055, 2897, 2844, 1612 cm^{-1}; UV (MeOH) λ_{max} 205, 235, 250 nm; EIMS *m*/*z* (rel int.) 366 $[M]^+$ (14), 333 $[M-H_2O-CH_3]^+$ (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 366.2024. $C_{24}H_{30}O_3$ requires 366.2195.

*4.2.4.2. Compound **7**.* IR (neat, KBr) ν_{max} 3255, 3027, 2977, 2954 cm^{-1}; UV (MeOH) λ_{max} 235, 260, 349 nm; EIMS *m*/*z* (rel int.) 298 $[M]^+$ (18), 280 $[M-H_2O]^+$ (75). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (5H, m, H-3′-H-7′), 6.70 (1H, s, H-6), 6.56 (1H, s, H-3), 5.70 (1H,

Table 2
^{13}C NMR data for compounds **6**, **8**–**19** (100 MHz in $CDCl_3$, signal $CDCl_3$ centred at δ 77.0 ppm)

	6	8	9	10	11	12	13	14	15	16	17	18	19
1	125.0	125.5	125.5	137.3	127.3	126.2	128.9	126.2	127.5	127.4	124.9	124.9	121.4
2	149.8	150.5	150.5	152.4	151.8	153.6	153.4	153.7	150.7	153.6	153.7	153.6	150.9
3	118.0	117.5	117.5	115.5	115.4	126.7	127.4	128.5	122.0	111.5	126.9	126.6	127.1
4	124.7	125.5	125.5	124.4	124.2	127.6	127.1	127.6	127.2	126.3	124.4	124.3	112.4
5	149.2	147.2	147.2	146.4	146.8	151.4	145.6	151.4	145.6	148.2	146.0	146.7	145.8
6	115.1	111.6	111.6	110.4	110.6	110.6	124.4	110.6	117.0	109.1	109.4	109.1	127.0
7	64.0	60.9	70.7	32.1	32.1	70.0	33.8	70.1	29.8	25.4	31.7	31.8	32.1
8	48.4	46.9	47.0	41.9	41.9	40.5	40.0	42.0	37.2	43.7	25.7	25.3	36.2
9	134.5	134.4	134.9	137.4	137.6	128.8	134.9	55.9	58.0	56.9	35.9	35.6	23.2
10	119.0	117.9	120.1	122.7	122.8	137.2	137.5	59.6	59.6	62.6	75.7	76.7	82.9
11	64.5	71.7	80.1	70.5	79.1	77.1	70.0	74.1	70.6	71.1	82.6	82.5	75.9
12	119.6	86.1	144.8	86.9	145.0	29.5[a]	29.3[a]	29.3[a]	27.6[a]	26.7[a]	23.1[a]	23.2[a]	23.2[a]
13	137.9	74.1	113.4	73.2	122.8	27.9[a]	28.3[a]	27.4[a]	27.5[a]	25.4	20.9	20.5[a]	21.1[a]
14	22.8	29.7	27.7	29.9	27.8	33.0	33.7	34.2	34.2	27.3	25.6	25.5	25.8
15	20.5	29.6	27.7	29.9	27.8	16.0	15.83	16.0	15.7	16.1	16.0	16.0	15.8
16	32.2	27.6	27.4	20.5	20.5								
17	16.6	16.2	16.1	16.3	16.2								
1′	73.4	74.0	74.2	72.3	70.6	81.7	80.7	79.9	80.7	70.5	70.4	70.6	
2′	134.6	137.6	137.2	137.6	137.6	143.2	143.2	143.2	142.1	137.8	137.6	137.1	
3′,7′	127.6	128.3	127.7	127.2	127.2	127.2	127.2	127.2	127.3	127.9	127.3	127.3	
4′,6′	127.8	127.3	128.4	128.3	128.3	128.3	128.3	128.3	128.1	128.7	128.4	128.4	
5′	127.6	127.6	127.2	127.3	127.3	128.6	128.6	127.6	127.7	127.4	127.7	127.7	

[a] Signals may be interchanged.

dddd, J=18, 10, 7.5, and 7.5, H-9), 5.17 (1H, d, J=18, H-10a), 5.14 (1H, d, J=10, H-10b), 5.02 (2H, s, H-1′), 2.75 (1H, dd, J=13.5, and 7.5, H-8a), 2.48 (1H, dd, J=13.5, and 7.5, H-8b), 2.23 (3H, s, H-12), 1.58 (3H, s, H-11). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (C-2), 149.5 (C-5), 133.6 (C-2′), 133.0 (C-9), 128.0 (C-1), 127.7 (C-4′,C-6′), 127.5 (C-5′), 127.4 (C-3′,C-7′), 126.6 (C-4), 119.8 (C-10), 119.6 (C-3), 111.2 (C-6), 71.3 (C-7), 71.3 (C-1′), 46.5 (C-8), 28.3 (C-11), 15.8 (C-12). HREIMS (M^+) found 298.1595. $C_{19}H_{22}O_3$ requires 298.1569.

*4.2.4.3. Compound **8**.* IR (neat, KBr) ν_{max}, 3478, 3275, 3034, 2987, 2934 cm^{-1}; UV (MeOH) λ_{max} 209, 235, 285 nm; EIMS m/z (rel int.) 364 $[M]^+$ (18), 323 $[M-C_3H_5]^+$ (65), 257 $[M-C_3H_5-C_5H_8]^+$ (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 298.1595. $C_{24}H_{28}O_3$ requires 298.1569.

*4.2.5. Reductive deoxygenation: 5-benzyloxy-4-methyl-2-(1,1-dimethylprop-2-yn-1-yl)oxy-1-(1-methylbut-3-en-1-yl)benzene (**10**) and 5-benzyloxy-9α,10α-epoxy-7β-11-heliannane (**16**)*

A solution of **8** (100 mg, 274 μmol) and triethylsilane (22 μL, 137 μmol) in dry dichloromethane (3 mL) was cooled down to −78 °C and treated dropwise with freshly distilled boron trifluoride etherate (34 μL, 274 μmol). The reaction mixture was stirred for 10 min at −78 °C and 30 min at −50 °C. Then, the reaction mixture was quenched by the addition of 3 mL of saturated solution of $NaHCO_3$, allowed to warm up to 5 °C, diluted with H_2O (5 mL), and thoroughly extracted with CH_2Cl_2 (4×). The combined extracts were washed (brine), dried (Na_2SO_4), and evaporated. The oily residue was purified by column chromatography (hexane/EtOAc 95:5) to furnish **10** (82%) as colourless oil.

Analogous treatment of **14** yielded **16** (62%).

*4.2.5.1. Compound **10**.* IR (neat, KBr) ν_{max} 3277, 3104, 2954, 2924 cm^{-1}; UV (MeOH) λ_{max} 209, 285 nm; EIMS m/z (rel int.) 348 $[M]^+$ (42), 282 $[M-C_5H_8]^+$ (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 348.2082. $C_{24}H_{28}O_2$ requires 348.2089.

*4.2.5.2. Compound **16**.* IR (neat, KBr) ν_{max} 2972, 2927 cm^{-1}; UV (MeOH) λ_{max} 205, 225, 285 nm; EIMS m/z (rel int.) 338 $[M]^+$ (30), 267 (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 338.1880, $C_{22}H_{26}O_3$ requires 338.1882.

*4.2.6. Ring closing metathesis reaction: preparation of 5-benzyloxy-7-hydroxy-7,11-heliann-9(10)-ene (**12**) and 5-benzyloxy-7,11-heliann-9(10)-ene (**13**)*

The diene **9** (855 mg, 2.33 mmol) was dissolved in 233 mL of gas free dichloromethane under Ar atmosphere. (Tricyclohexyl)-phosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene][benzylidene]ruthenium(IV) dichloride (197 mg, 233 μmol) was added and the resulting mixture was stirred for 1 h at room temperature. The reaction flask was opened to deactivate Grubbs' catalyst and stirred for an additional hour. The solvent was removed by evaporation and chromatographed (hexane/AcOEt, 19:1), yielding compound **12** (90%).

This procedure using **11** as starting material afforded **13** (91%).

*4.2.6.1. Compound **12**.* IR (neat, KBr) ν_{max} 3469, 2976, 2926 cm^{-1}; UV (MeOH) λ_{max} 209, 220, 280 nm; EIMS m/z (rel int.) 338 $[M]^+$ (15), 320 $[M-C_5H_8]^+$ (35), 229 $[M-C_7H_7]^+$ (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 338.1869. $C_{22}H_{26}O_3$ requires 338.1882.

*4.2.6.2. Compound **13**.* IR (neat, KBr) ν_{max} 2961, 2926, 1499 cm^{-1}; UV (MeOH) λ_{max} 215, 280 nm; EIMS m/z (rel int.) 322 $[M]^+$ (70), 231 $[M-C_7H_7]^+$ (85), 177 (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 322.1922. $C_{22}H_{26}O_2$ requires 322.1933.

*4.2.7. Stereoselective epoxidation: preparation of 5-benzyloxy-7-hydroxy-9α,10α-epoxy-7,11-heliannane (**14**) and 5-benzyloxy-9α,10α-epoxy-7βH,11-heliannane (**15**)*

To an acetonitrile solution (6 mL) of **12** (217 mg, 0.64 mmol) was added an aqueous Na_2·EDTA solution (3.2 mL, 4×10^{-4} M). The homogeneous solution was cooled to −2 °C, followed by addition of methyl trifluoromethyl ketone (0.7 mL) via a precooled syringe. To this solution was added a mixture of $NaHCO_3$ (554 mg, 6.6 mmol) and OXONE® (2.478 g, 4.03 mmol) in five portions during an hour, and, then, water was added and extraction with dichloromethane was carried out (3×). The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (4:1), yielding **14** (82%).

When this procedure was carried out on **13** it afforded **15** (72%).

*4.2.7.1. Compound **14**.* IR (neat, KBr) ν_{max} 3465, 2981, 2924 cm^{-1}; UV (MeOH) λ_{max} 209, 220, 280 nm; EIMS m/z (rel int.) 354 $[M]^+$ (40), 336 $[M-H_2O]^+$ (8). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 354.1829. $C_{22}H_{26}O_4$ requires 354.1831.

*4.2.7.2. Compound **15**.* IR (neat, KBr) ν_{max} 2925, 2914, 1500 cm^{-1}; UV (MeOH) λ_{max} 205, 215, 280 nm; EIMS m/z (rel int.) 338 $[M]^+$ (35), 267 (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 338.1891. $C_{22}H_{26}O_3$ requires 338.1882. Mp 126–129 °C.

*4.2.8. Reductive opening of oxirane ring: preparation of 5-benzyloxy-10α-hydroxy-7αH,11-heliannane (**17**) and 5-benzyloxy-10α-hydroxy-7βH,11-heliannane (**18**)*

To a stirred suspension of $LiAlH_4$ (123 mg, 3.25 mmol) in THF (3 mL) at 0 °C, a solution of **16** (100 mg, 295 μmol) in THF (1 mL) was added. The reaction mixture was stirred for 5 h and a mixture of water and diethylether (1:1) was then added and stirred for an hour. The reaction mixture was filtered through Celite, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (9:1), yielding **17** (71%).

When this procedure was carried out on **15** it afforded **18** (75%).

*4.2.8.1. Compound **17**.* IR (neat, KBr) ν_{max} 3464, 2933, 2924, 1499 cm^{-1}; UV (MeOH) λ_{max} 205, 280 nm; EIMS m/z (rel int.) 340 $[M]^+$ (36), 151 (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 340.2055. $C_{22}H_{28}O_3$ requires 340.2038.

*4.2.8.2. Compound **18**.* IR (neat, KBr) ν_{max} 3450, 2926, 2914, 1500 cm^{-1}; UV (MeOH) λ_{max} 205, 280 nm; EIMS m/z (rel int.) 340 $[M]^+$ (36), 151 (100). ^{1}H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 340.2054. $C_{22}H_{28}O_3$ requires 340.2038. Mp 65–68 °C.

*4.2.9. Deprotection of hydroxyl group: preparation of 5-hydroxy-10α-hydroxy-7αH,11-heliannane (**19**) and (±)-heliannuol A (**20**)*

Pd/C catalyst (50 mg) was added to a solution of **17** (100 mg, 293 μmol) in dichloromethane (10 mL) and stirred for 3 h under hydrogen atmosphere (1 atm). The reaction mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatography using hexane/EtOAc (4:1), yielding **19** (98%).

When this procedure was carried out on **18** it afforded **20** (99%).

4.2.9.1. Compound ***19***. IR (neat, KBr) ν_{max} 3390, 2927, 2914, 1500 cm^{-1}; UV (MeOH) λ_{max} 205, 275, 290 nm; EIMS *m*/*z* (rel int.) 250 $[M]^+$ (27), 151 (100). ^1H NMR, see Table 1. ^{13}C NMR, see Table 2. HREIMS (M^+) found 250.1581. $C_{15}H_{22}O_3$ requires 250.1569.

5. Supplementary data

CCDC 676889 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223 336033; email: deposit@ccdc.cam.ac.uk].

Acknowledgements

This research was supported by the Ministerio de Educación y Ciencia, Spain (MEC; AGL2005-05190/AGR).

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