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Total Syntheses of Four Stereoisomers of 4α-Hydroxy-1β,7β-peroxy-10βH-guaia-5-ene

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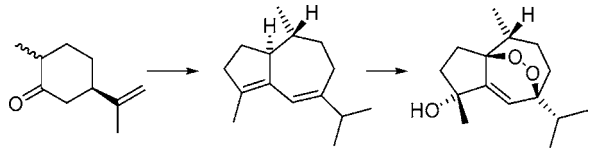
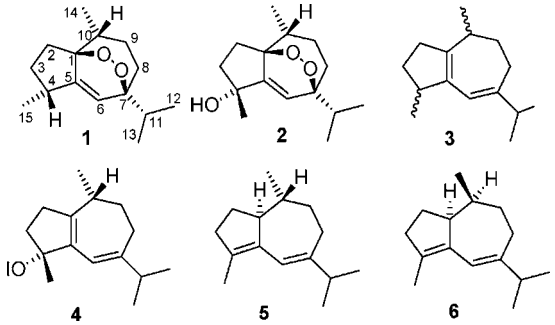
ABSTRACT



The first total syntheses of four stereoisomers of 4α-hydroxy-1β,7β-peroxy-10βH-guaia-5-ene are reported starting from the readily available (+)-dihydrocarvone. These compounds have been synthesized from dienes (–)-isoguaiene and (–)-10-*epi*-isoguaiene by tandem *ene* hydroperoxylation-[4 + 2] cycloaddition with O_2 followed by selective reduction. The structure of the natural 4α-hydroxy-1β,7β-peroxy-10βH-guaia-5-ene isolated from *Liabum floribundum* has been confirmed.

From the discovery of the antimalarial drug artemisinin, peroxy compounds have generated a great interest due to their range of biological activities,[1] and hence a significant work in the synthesis of these compounds has resulted.[2] In the sesquiterpene group, two 1β,7β-peroxyguaia-5-ene derivatives **1** and **2** have been isolated from natural sources. Compound **1** was reported as natural product in 1998 for the first time by Hirota and co-workers as an antifouling component from an *Axinyssa* sponge;[3] however, it had been described two years before by Faulkner and co-workers as a reaction product with a singlet oxygen of an antimicrobial (−)-1,6-guaiadiene (**3**) isolated from an *Halichondria* sponge,[4] whose stereochemistry was not determined. On the other hand the 4α-hydroxyl derivative **2** was isolated[5] by Bohlmann and co-workers from *Liabum floribundum* (Compositae). These authors suggested a biosynthetic pathway to compound **2** through 4-hydroxy-$\Delta^{1-5,6}$-diene **4**, which should be formed by a reaction of a $\Delta^{4,6}$-diene precursor with singlet oxygen. In view of the relative stereochemistry of **2**, compounds **5** or **6** (or their enantiomers) should be this $\Delta^{4,6}$-diene precursor.



This hypothesis is strongly supported by the fact that both dienes **5** and **6** are known natural products that have been

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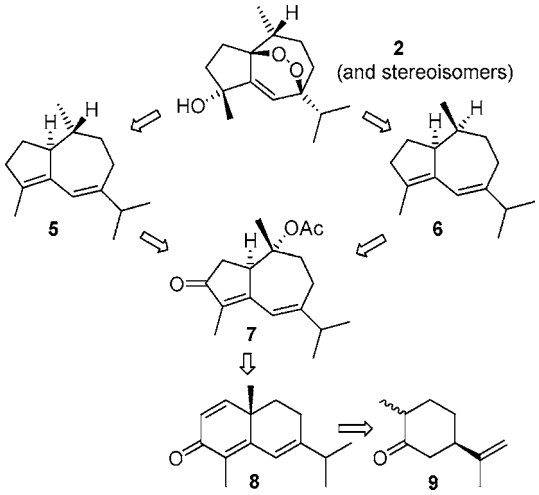
isolated by Bohlmann and co-workers from other Compositae sp. Structure **6** was assigned to (+)-isoguaiene isolated from *Parthenium hysterophorus*,[6] while structure **5** (or its enantiomer) was assigned to a (−)-stereomer isolated from *Athanasia dregeana*.[7] Later, both dienes were also reported as components of several liverworts. Thus, (−)-**6** has been identified (chiral GC) in *Dumortiera hirsuta*,[8] and compounds **5** and **6** have been isolated from *Bryopteris filicina*[9] and *Pellia epiphylla*,[10] respectively. Besides, Friedel and Matusch have reported[11] $[\alpha]_D$ values and NMR data of (+)-**5** and (−)-**6** obtained from the acid isomerization of (+)-γ-gurjunene. Unfortunately, these authors do not make any reference to the previously isolated natural products, and the solvents that they used do not allow a comparison with the published data for natural **5** and **6**.

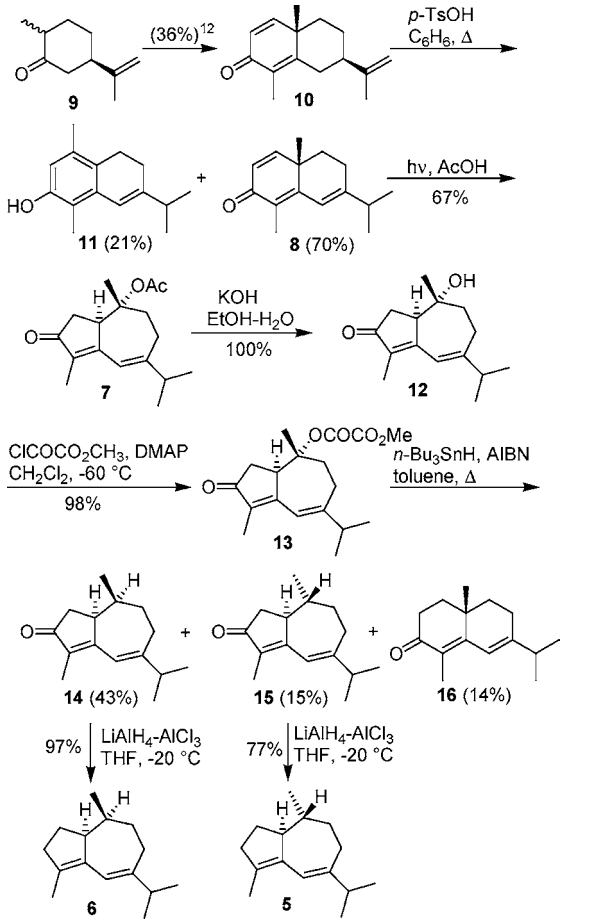
In this Letter, we report the enantioselective syntheses of four stereoisomers of 4α-hydroxy-1β,7β- peroxy-10βH-guaia-5-ene, one of them being natural product **2**. Retrosynthetic analysis (Scheme 1) suggested that **2** and its stereoisomers could be prepared from **5** or **6** via tandem ene hydroperoxylation-[4 + 2] cycloaddition with singlet oxygen followed by selective reduction of the hydroperoxide. In turn, the intermediate dienes **5** and **6**, could be prepared by C-3 and C-10 deoxygenation of guaiadienone **7**, which is easily obtained by photochemical rearrangement of trienone **8**. This compound is easily available from (+)-dihydrocarvone (**9**).

Scheme 1. Retrosynthetic Analysis



The synthetic sequence from (+)-dihydrocarvone (**9**) to **5** and **6** is depicted in Scheme 2. The transformation of **9** into 1,2-dehydro-α-cyperone (**10**) has been carried out following the procedure described by de Groot and co-workers[12] with a 36% global yield. Treatment of **10** with *p*-TsOH in benzene at reflux afforded **8**[13] in 70% yield (along with 21% of the rearranged product **11**).[14] Irradiation of **8** in AcOH with UV light[15] brought about rearrangement of eudesmane to the guaiane skeleton to give the key intermediate **7** in 67% yield.

Scheme 2. Syntheses of Guaiadienes **5** and **6**



Deoxygenation at C-10 of **7** was carried out through its methyl oxalate derivative.[16] Base hydrolysis of the acetate group followed by reaction of the parent alcohol **12** with ClCOCOOCH$_3$−DMAP afforded methyl oxalate derivative **13**, which upon radical deoxygenation with *n*-Bu$_3$SnH−AIBN gave a mixture of two epimeric guaiadienones (−)-**14**[17] (43%) and (−)-**15**[17] (15%), as well as (+)-β-cyperone (**16**)[12] (14%). The stereochemistry at C$_{10}$ in **14** and **15** was established by NOE experiments. Compound **14** showed a positive NOE between H$_1$ and H$_{10}$, whereas in **15** the positive effect was observed between H$_1$ and H$_{14}$. The formation of

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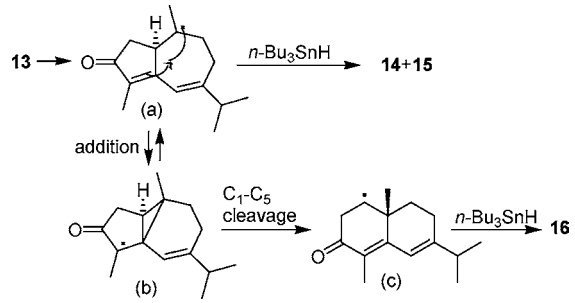
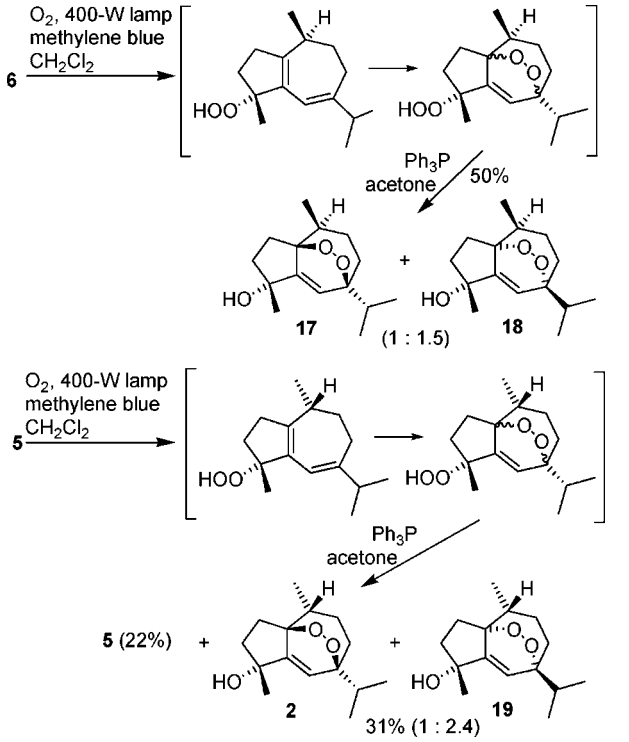
Scheme 3. Plausible Mechanistic Pathway for the Formation of (+)-β-Cyperone (**16**)



Scheme 4. Syntheses of 4α-Hydroxy-1,7-peroxy-10*H*-guaia-5-enes



the three reaction products could be explained through the radical intermediate a (Scheme 3). Guaiadienones **14** and **15** should arise by attack of the reagent from either the α-(preferred) or β-face, respectively. On the other hand, the eudesmenone **16** should arise by intramolecular radical addition in intermediate a to give the tricyclic intermediate b, followed by cleavage of the C_1-C_5 bond to afford c and subsequent reaction with the reagent. To the best of our knowledge, this is the first time that a radical rearrangement from guaiane to eudesmane framework has been reported.

Deoxygenation at C_3 of dienone **14** by treatment with $LiAlH_4-AlCl_3$[18] at −20 °C afforded diene **6** {$[\alpha]^{26}_D$ −45.9 (Cl_3CH)} in excellent yield (97%). The spectral data of synthetic **6** were coincident with those reported[6] for natural (+)-isoguaiene. However, from their opposite optical rotation signs, it follows that natural (+)-isoguaiene, $[\alpha]^{24}_D$ +36 (Cl_3CH), isolated from *P. hysterophorus* has the opposite absolute stereochemistry, and consequently (−)-isoguaine isolated from *D. hirsuta*[8] has absolute stereochemistry as depicted in **6**. By the same procedure, dienone **15** afforded diene **5** (77%), which exhibited identical spectral data and optical rotation signs {$[\alpha]^{24}_D$ −63.1 (Cl_3CH), lit.[7] $[\alpha]_D$ −27.5 (Cl_3CH)} to those reported for the natural guaiadiene isolated from *A. dregeana*.[7]

Finally, we carried out the synthesis of compounds **2** and **17**−**19**. A tandem hydroperoxylation/Diels−Alder cycloaddition with the singlet oxygen[19] of diene **6** (Scheme 4) followed by selective reduction of the C_4-hydroperoxide group afforded 4α-hydroxy peroxyguaienes **17** and **18** in a 1:1.5 ratio and 50% yield. By the same procedure, from diene **5** two new 4α-hydroxy peroxyguaienes, **2** and **19**, were obtained in 31% yield and 1:2.4 ratio, 22% of the starting material being recovered (Scheme 4). Their stereochemistry was assigned by NOE experiments in DMSO-d_6 for **2** and **17** and in Cl_3CD for **18** and **19**. A positive NOE between the OH group and the $C_{10}-CH_3$ in **2** or H_{10} in **17** agrees with an α-disposition for the OH group and a β-peroxo bridge. For compounds **18** and **19**, the positive NOE observed between the C_4-CH_3 and $C_{10}-CH_3$ in **18** or H_{10} in **19** agree with a β-disposition of the C_4-CH_3 (4α-OH) and an α-peroxo bridge. Compound **2** exhibited identical spectral data to those reported for the natural hydroxy peroxo guaiene isolated from *L. floribundum*.[5] However, comparison of their optical rotations and hence confirmation of the absolute stereochemistry of the natural product was not possible, as the optical rotation value for the natural product has not been reported.

The high stereoselectivity in the *ene* hydroperoxylation in compounds **5** and **6** (Scheme 4) must result from the α disposition of allylic H_1 in both dienes, which determines the orientation of $^1O_2$ attack,[20] giving only 4α-hydroperoxy-1,6-dienes. The subsequent Diels−Alder cycloaddition was less stereoselective, affording mixtures of α- and β-endoperoxides, which agrees with the results reported[4] by Faulkner and Sullivan for diene **3**.

In conclusion, we have accomplished the first total syntheses in enantiomerically pure form of four stereoisomers of 4α-hydroxy-1β,7β-peroxy-10β*H*-guaia-5-ene, one of them being identical to natural product **2**. These compounds have been synthesized in a straightforward way involving a tandem ene hydroperoxylation-[4 + 2]cycloaddition with singlet oxygen followed by selective reduction from the dienes (−)-10-*epi*-isoguaiene (**5**) and (−)-isoguaiene (**6**). In turn, these dienes have been prepared from the readily available (+)-dihydrocarvone (**9**). The synthesis of these compounds has allowed us to establish the stereostructures of natural products **2**, **5**, and **6** and the absolute configuration of dienes **5** and **6**.

Acknowledgment. Financial support from the European Commision (FAIR CT96-1781) is gratefully acknowledged.

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Supporting Information Available: Experimental procedures, characterization data for all compounds, ^{1}H NMR and ^{13}C NMR spectra of all compounds, and NOE experimets for compounds **2**, **14**, **15**, and **17**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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