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# Quesnoin, a Novel Pentacyclic *ent*-Diterpene from 55 Million Years Old Oise Amber

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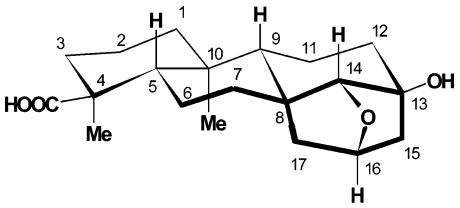


Quesnoin (**1**)

Amber, fossilized tree resin, found at the Oise River area of the Paris basin (France) was dated as being 55 million years old. Quesnoin, a novel unique pure organic compound, was isolated from Oise amber. $^{1}$H and $^{13}$C NMR spectroscopic analysis indicated an unknown diterpene skeleton, quesnane. The absolute configurations of the eight chiral centers of quesnoin were determined to be 4*S*, 5*S*, 8*R*, 9*S*, 10*S*, 13*S*, 14*R*, and 16*S* by chiral auxiliary (*R*)- and (*S*)-phenylglycine methyl ester derivatization. Quesnoin allowed us to disclose the tree producer, corresponding to modern *Hymenaea oblongifolia*, Fabaceae, a subfamily of Caesalpiniaceae, one of the oldest angiosperm. The presence of the Amazon rainforest tree, *H. oblongifolia*, indicated that the climate of the Paris basin might have been tropical in the early Eocene period, 55 million years ago.

## Introduction

A new amber fossil deposit was discovered, in 1997, at the Quesnoy locality in the Oise River area of the Paris basin (France). The deposit is exceptionally rich in diversity with flora, fauna, and especially amber fossils and by an excellent state of preservation.[1,2] The earliest Eocene age, about 53−55 million years ago, of the deposit was assessed by stratigraphy and confirmed by the presence of fossil remains of *Condylarthra* (primitive ongulet), *Perissodactyla* (small equidae), and *Teihardina* (minuscule primate) as the mammalian layer reference.[3] The Oise amber clusters contained more than 300 arthropod species, which are of great importance for insect evolution study[4] (Figure 1) and angiosperm-like pollens and woody remains mainly belonging to dicotyledon.[2,5,6] It is noteworthy that London Clay is also very rich in diverse flora fossils aged the same (early lower Eocene).[7,8] Generally, it is very difficult to identify the tree producer of resin that eventually becomes

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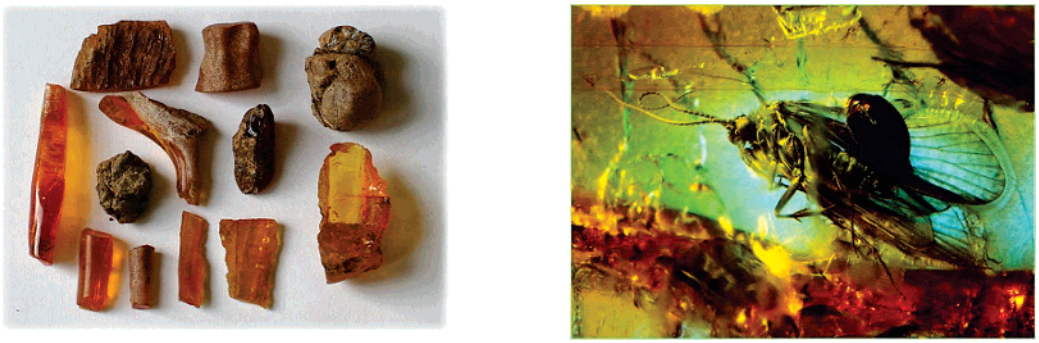


**FIGURE 1.** Oise ambers and insect inclusion (Trichoptera) in Oise amber.

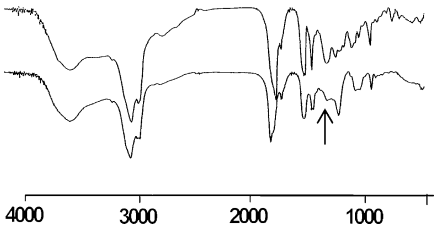



**FIGURE 2.** IR spectra in KBr pellet of Oise amber (upper) and Baltic amber (lower).

amber, which contains numerous ditepene isomers. Here, we report discovery of quesnoin (**1**), a key unknown organic compound isolated from Oise amber, which might indicate the tree producer of the Oise amber.

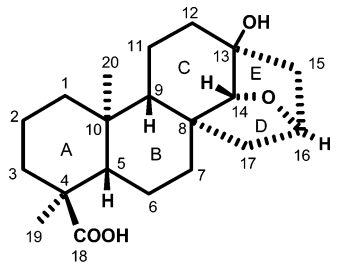
## Results and Discussion

The Oise amber was compared first with Baltic amber, aged 30−40 million years old, and gymnosperm origin,[9,10] for geographical neighboring reasons and for the most important reference of European ambers in the Palaeogene period.

The infrared (IR) spectra (KBr pellet) of the two ambers differed in the fingerprint regions ($\nu$ 1700−500 $cm^{-1}$), and the Oise amber spectrum (Figure 2, upper) showed a large intense band at $\nu$ 1260 $cm^{-1}$, instead of a characteristic shoulder of Baltic amber (Figure 2, lower).

The major part of exuded tree resin undergoes, via free radical mechanism, intermolecular polymerization and cross-linking to produce solid-state copal and amber.[11−13] The minor part consists of 10−30% soluble matter in organic solvents and remains in a complex mixture of monomers transformed by oxidation, cyclization, and rearrangement. We made the assumption that the freshly exuded resin should contain the marker compounds produced by the living tree. Then, we investigated the dichloromethane extract of the amber, whereas the amber research was, usually, focused on solid polymer by means of solid-state $^{13}C$ NMR analysis. The liquid-state $^{13}C$ NMR *J* modulated spectra (75 MHz, in $CDCl_3$; $CH_3$ and CH signals were drawn on the upper side and $CH_2$ and C on the lower side of the spectra) of the dichloromethane extract of Oise and Baltic ambers showed clear differences between the two ambers (Figure 3).

The main differences observed were that the Oise amber (Figure 3A) displayed only one major carbonyl signal at $\delta$ 185 as well as a small signal of exocyclic methylene carbons, >C=$CH_2$, at $\delta$ 106 and $\delta$ 148, whereas the Baltic amber spectrum (Figure 3B) showed several carbonyl signals centered at $\delta$ 172, $\delta$ 177, and $\delta$ 185 and vinyl carbons at $\delta$ 106, $\delta$ 110, and $\delta$ 145. The optical activities of dichloromethane extract were opposite between Oise amber, $[\alpha]^{D}_{20}$ −26° (*c* 1, MeOH), and Baltic amber, $[\alpha]^{D}_{20}$ +16.6° (*c* 1, MeOH). Hence, the trees that produced the Oise amber and the Baltic amber were clearly not the same.




Quesnoin (**1**)

Then, we attempted to isolate some organic marker compounds. The $CH_2Cl_2$ extract of the Oise amber afforded a unique isolable pure new compound **1**, which we named quesnoin, by repeated chromatography followed by purification on TLC.

Quesnoin (**1**) crystallized as needles ($CHCl_3$−MeOH), mp 177 °C, and possessed an optical activity with specific rotation $[\alpha]_D^{20}$ +5.3° (*c* 1, MeOH). The high-resolution electrospray mass spectrum of **1** presented a protonated molecular ion $[M + H]^+$ at *m*/*z* 335.2201, corresponding to the molecular formula $C_{20}H_{30}O_4$, and the $^1H$ and $^{13}C$ NMR data (Table 1), indicated six degrees of unsaturation. The $^{13}C$ NMR spectrum ($CDCl_3$) showed one carbonyl signal at $\delta$ 182.7 in the $sp^2$ carbon region, accounting for one unsaturation. The absence of other $sp^2$ carbon signals suggested that the five remaining unsaturations might be attributed to five saturated rings.

The $^1H$ NMR, $^{13}C$ NMR, and HSQC spectra indicated further the presence of two methyls, nine methylenes, four methines, and four quaternary carbons. The NMR spectral features, in which a major part of the proton signals was concentrated in the aliphatic region, suggest tricyclic diterpene as a basic structure.

The $^1H-^1H$ COSY spectrum with heavily overlapped proton signals allowed identification of only three spin systems. A proton at $\delta$ 4.50 correlated with protons of $CH_2$15 and $CH_2$17, forming the oxygenated propylene fragment (**a**), a proton at $\delta$

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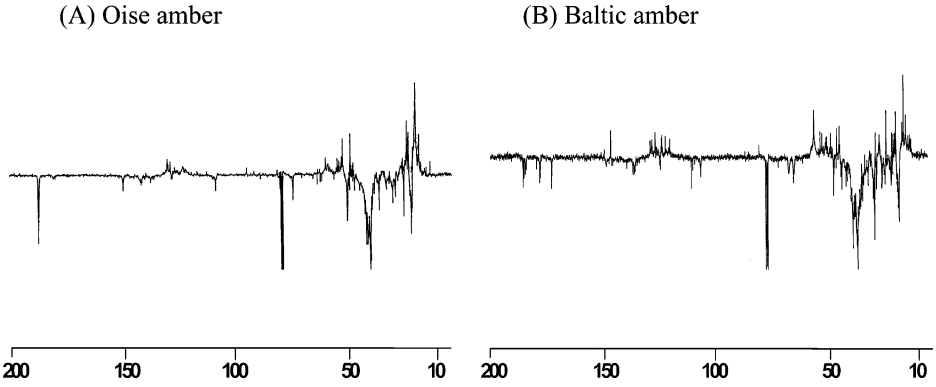



**FIGURE 3.** $^{13}C$ NMR spectra (75 MHz, in $CDCl_3$) of dichloromethane extract of Oise amber (A) and Baltic amber (B).

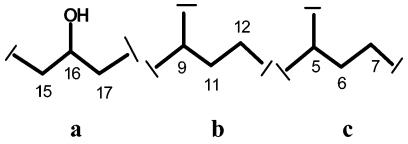
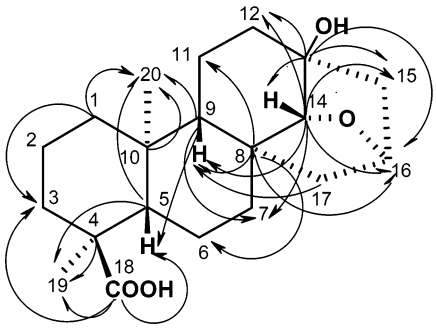



**FIGURE 4.** Structural fragments of **1**.




C→ H

**FIGURE 5.** Main HMBC correlations of Quesnoin (**1**).

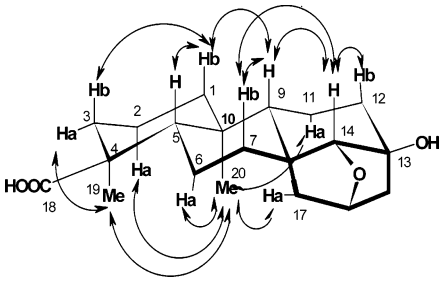



**FIGURE 6.** Selected NOE interactions of **1**.

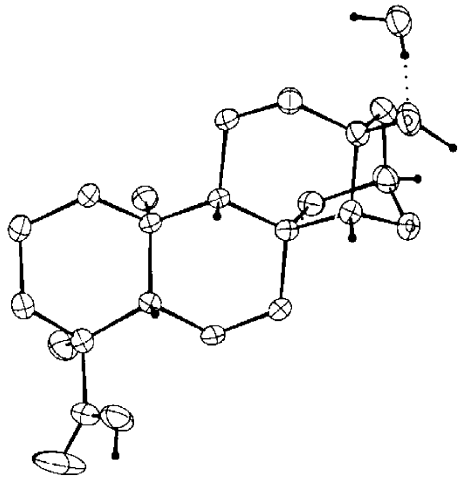


**FIGURE 7.** Molecular structure of quesnoin (**1**).

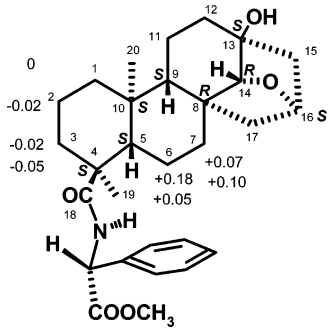



**FIGURE 8.** Absolute configuration of quesnoin-(*R*)-PGME amide (**1R**) deduced from chemical shift increments ($\Delta\delta_H = \delta$ **1S** $- \delta$ **1R**).

1.92 of CH12 coupled with $CH_2$11 correlated with H9, forming 9-substituted propylene fragment (**b**), and $CH_2$6 presented cross-peaks with $CH_2$7 and CH5, making another 5-substituted propylene fragment (**c**) (Figure 4).

HMBC multi-bond correlation analysis allowed the detection of one ring **B** from fragment **c**, H9 of fragment **b**, and two quaternary carbons at $\delta$ 37.2 and 44.3 with the help of the two methyl groups. The quaternary carbon at $\delta$ 44.3 was correlated with H9 and Ha11 of fragment **b** and with Ha6 and Ha7 of fragment **c**, thus assigned to C8, connecting two fragments **b** and **c** (Figure 5). CH at $\delta$ 51.9 of fragment **b** was correlated with H5 and Ha7, forming ring **B**. CH at $\delta$ 50.1 of fragment **c** correlated with two methyl protons, whereas CH at $\delta$ 51.9 presented a cross-peak only with methyl protons at $\delta$ 0.78. Thus, CH at $\delta$ 50.1 of fragment **c** was attributed to position 5 and CH at $\delta$ 51.9 of fragment **b** to position 9, and the methyl at $\delta$ 0.78 was connected to carbon 10 and the methyl at $\delta$ 1.11 to carbon 4 of decalin rings **A** and **B**. The correlation of C17 with H9 allowed the connection of C17 of fragment **a** to C8. Oxygenated CH14 at $\delta$ 93.1 presented the following cross-peaks: first with H9 and Hb7, so this carbon was fixed to C8; second with Ha12, forming ring **C**; third with oxygenated CH16 proton, indicating the presence of a tetrahydrofuran ring **D**; and finally with Ha15, linking the last ring **E**. The quaternary hydroxyl carbon at $\delta$ 77.9 was correlated with Hab12, H14, Hb15, and H16, taking place at an angular C13 position. Concerning the chemical shifts of ring **A**, the $CH_2$ carbon at $\delta$ 38.3 was correlated with methyl-20 protons at $\delta$ 0.78 and Ha3

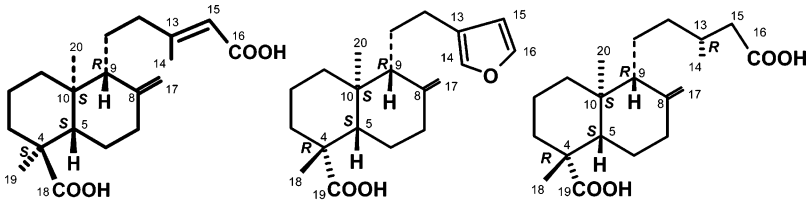



**FIGURE 9.** Structures and absolute configurations of *ent*-labdane-type compounds: (A) guamaic acid, (B) daniellic acid, and (C) oliveric acid.

**TABLE 1. $^1$H and $^{13}$C NMR Spectroscopic Data ($CDCl_3$) for Quesnoin (1), (*R*)-PGME Amide (1R), and (*S*)-PGME Amide (1S)**

| | **1** | | | **1**R | | **1**S | |
|---|---|---|---|---|---|---|---|
| | $\delta_C$ | HMBC (H no.) | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ |
| **1a** | 38.3 | **3a**, **20** | 1.68 m | 38.2 | 1.68 m | 38.0 | 1.68 m |
| **1b** | | | 0.99 m | | 1.01 m | | 1.01 m |
| **2a** | 17.8 | | 1.57 m | 17.9 | 1.55 m | 17.9 | 1.53 m |
| **2b** | | | 0.97 | | 1.01 m | | 1.01 m |
| **3a** | 36 | **1**9 | 1.55 m | 36.9 | 1.49 m | 37.1 | 1.44 m |
| **3b** | | | 1.70 m | | 1.74 m | | 1.72 m |
| **4** | 47.2 | **3b**, **5**, **19** | | 47.1 | | 47.2 | |
| **5** | 50.1 | **3a**, **7a**,**b**, **19**, **20** | 1.68 m | 51.0 | 1.63 m | 51.0 | 1.66 m |
| **6a** | 20.6 | **5**, **7b** | 1.33 m | 19.9 | 1.22 m | 20.0 | 1.27 m |
| **6b** | | | 1.08 m | | 0.93 m | | 1.11 m |
| **7a** | 40.5 | **6**, **5**, **14** | 1.75 | 40.4 | 1.65 m | 40.6 | 1.75 m |
| **7b** | | | 1.33 m | | 1.23 m | | 1.30 m |
| **8** | 44.3 | **6a**, **7a**, **9**, **11a**, **17a** | | 44.2 | | 44.2 | |
| **9** | 51.9 | **1b**, **5**, **7a**, **11b**, **12a**, **17a**, **20** | 1.08 m | 51.9 | 1.07 m | 52.0 | 1.10 m |
| **10** | 37.2 | **2a**, **5**, **6a**, **9**, **20** | | 37.4 | | 37.4 | |
| **11a** | 17.9 | **9**, **12a**,**b** | 1.62 m | 18.0 | 1.03 m | 18.0 | 1.05 m |
| **11b** | | | 1.05 m | | 1.62 m | | 1.64 m |
| **12a** | 32.4 | **11**, **15a** | 1.92 dm 10.6 | 32.3 | 1.93 dm 13.1 | 32.1 | 1.94 dm 13.1 |
| **12b** | | | 1.47 m | | 1.47 m | | 1.49 m |
| **13** | 77.9 | **12a**,**b**, **14**, **15b**, **16** | | 78.1 | | 78.1 | |
| **14** | 93.1 | **7b**, **9**, **12a**, **15a**, **16** | 3.38 s | 92.9 | 3.32 s | 92.9 | 3.35 s |
| **15a** | 46.8 | **12b**, **14**, **17a**,**b** | 1.57 m | 47.1 | 1.58 m | 47.0 | 1.59 m |
| **15b** | | | 1.69 m | | 1.67 m | | 1.68 m |
| **16** | 77.6 | **14**, **17b** | 4.50 t 5.0 | 77.5 | 4.49 t 5.3 | 77.5 | 4.49 t 5.3 |
| **17a** | 37.2 | **9**, **15a** | 1.36 m | 37.2 | 1.34 m | 37.2 | 1.36 m |
| **17b** | | | 1.28 m | | 1.24 m | | 1.27 m |
| **18** | 182.7 | **3b**, **5**, **19** | | 178.0 | | 178.0 | |
| **19** | 16.4 | **3a**,**b**, **5** | 1.09 s | 16.5 | 1.18 s | 16.5 | 1.18 s |
| **20** | 15.7 | **1**, **5**, **9** | 0.78 s | 15.9 | 0.80 s | 15.9 | 0.82 s |
| NH | | | | | 6.68 d 6.6 | | 6.70 d 6.6 |
| CH | | | | 56.8 | 5.51 d 6.6 | 56.8 | 5.50 d 6.6 |
| COOMe | | | | 171.6, 52.7 | | | 3.70 s |
| Ph | | | | 136.8, 127.3, 128.9, 128.5 | | 7.27−7.38 m | |

at $\delta$ 1.55, so assigned to C1. The carbonyl carbon at $\delta$ 182.7, giving cross-peaks with methyl-19 protons, Hb3 and H5, was attributed to the C18 carboxylic acid.

Quesnoin (**1**) was revealed to possess unprecedented tetracyclic diterpene linkage with oxabicycles **D** and **E**. We propose the name quesnane for this novel tetracyclic skeleton. The relative configuration was determined further by analysis of NOESY $^1$H−$^1$H dipole−dipole interactions locating the relative spatial position of the protons (Figure 6). Me-20 interacted with Me-19, Ha11, Ha6, Ha2, and Ha17. All these protons were situated on one side of the molecular plane. H14 interacted with Hb7, H9, and Hb12, and Hb1 was correlated with Hb3, H5, and H9. Thus, these protons were located on another side of the molecular plane. This extraordinary structure of quesnoin (**1**) and the relative configuration were confirmed by X-ray diffraction analysis of a single parallelepiped crystal (Figure 7).

The absolute configuration of quesnoin (**1**) was further determined with respect to chiral (*R*)- and (*S*)-phenylglycine methyl ester (PGME) groups introduced into the molecule.[14] NH of both (*R*)-phenylglycine amide (**1R**) and (*S*)-amide (**1S**) presented NOE interactions with Me-19 protons, closely located to these protons as shown in Figure 8. $^1$H NMR analysis (Table 1) to observe the anisotropic effects resulted in a strong upfield shielding of $\delta$ 0.05 to 0.18 ppm of H6 and H7 finding in the magnetic field induced by benzene ring current in quesnoin-(*R*)-PGME amide (**1R**) (Figure 8), as compared to that of (*S*)-PGME amide (**1S**). H6a,b and H7a,b showed high positive shifting values ($\Delta\delta_H = \delta$ **1S** $-\ \delta$ **1R**) of, respectively, +0.05, +0.18, +0.10, and +0.07. Thus, these protons must be located on the right side of the PGME-C4−-$CH_3$19 axis, and H2a and H3a,b displayed negative values of $\Delta\delta_H$, respectively, −0.02, −0.05, and −0.02, situated on the left side, as shown in Figure 8. Hence, the chirality of C4 is *S*. Thus, quesnoin (**1**) was revealed to possess the absolute configuration 4*S*, 5*S*, 8*R*, 9*S*, 10*S*, 13*S*, 14*R*, and 16*S*.

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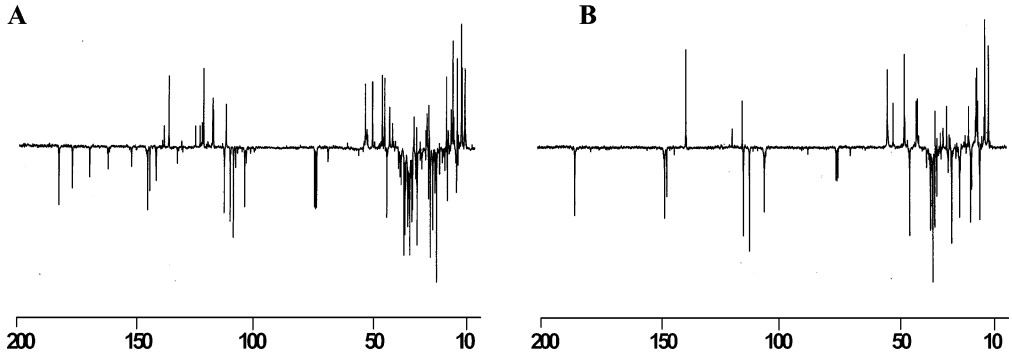
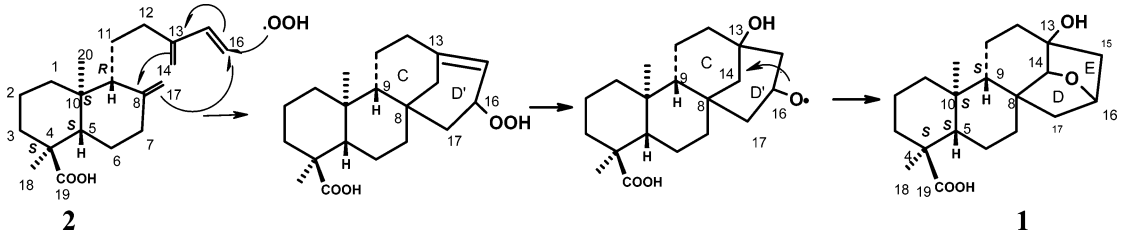
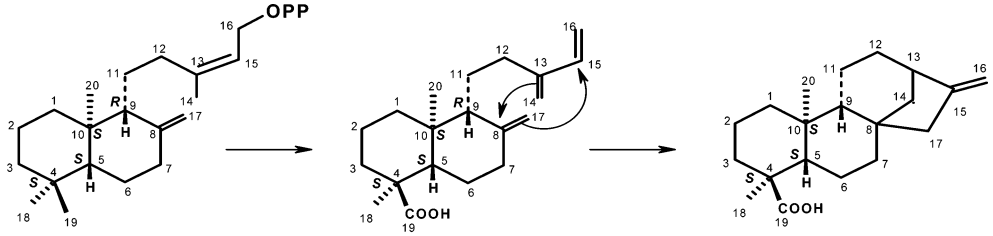



**FIGURE 10.** $^{13}C$ NMR spectra (75 MHz, in $CDCl_3$) of dichloromethane extract of fresh resins: (A) *H. courbaril* and (B) *H. oblongifolia*.

**SCHEME 1. Hypothesis for Chemical Pathway to Produce Quesnoin (1)**




**SCHEME 2. Common Cyclization of *ent*-Copalyl Diphosphate to *ent*-Kaurene-Type Skeleton**




Then, the chemical pathway to produce quesnoin (**1**) was examined (Scheme 1). The conjugated hexa-*S*-*cis*-diene side chain and the exocyclic vinyl (>C8 = $CH_2$17) of labdane compound **2** in the exuded resin might undergo Diels−Alder concerted cycloaddition initiated by a peroxy radical under high pressure and high temperature of geological conditions to form two rings: **C** and **D′**. The C13−C15 bridge head double bond, which must be quite strained, might first be hydrated to loosen ring **D′**. Then, the 16-oxy radical bound to C-14 at a favorable $\delta$ position, forming bicyclic tetrahydrofurane rings **D** and **E**. An alternative mechanism would involve a similar intramolecular Diels−Alder reaction of a furan derivative with a C8−C17 double bond of daniellic acid (Figure 9B)[15a] and polyalthic acid isolated from *Polyalthia fragrans* (Anonaceae)[15b] and *Eupatorium buniifolium* (Asteraceae).[15c]

However, it seems that the furano-diterpenes are too stable to undergo further cycloaddition.[15d] Therefore, quesnoin (**1**) might be formed as a byproduct of the polymerization process by cycloaddition from *ent*-labdane diterpene possessing 4*S*, 5*S*, 9*S*, and 10*S* configurations. Hence, the isoozic acid (**2**)[16a] matching the required absolute configuration should be the precursor of quesnoin (**1**).

However, this type of cyclization has been observed for the first time among natural product synthesis. In fact, by passing one of the biosynthetic pathways, the *ent*-copalyl diphosphates commonly undergo enzymatic cyclization into widely occurring natural *ent*-kaurene linkages by the action of labdane-related diterpene synthases.[16b] It is rather *S*-*trans*-diene compounds that are concerned in this process (Scheme 2).

Fossils of trees exuding a resin were also found in the same Oise deposit. The microscopic analysis suggested that the tree fossil might correspond to the modern genus *Daniellia*, Caesalpiniaceae, angiosperm.[6] However, our chemical molecular work indicated rather the genus *Hymenaea*, Caesalpiniaceae. In fact, isoozic acid (**2**)[16a] and guamaic acid[17] (Figure 9A) isolated from the *Hymenaea* species possess the absolute configuration 4*S*, 5*S*, 9*R*, and 10*S* that we have confirmed by derivatization to be an amide with auxiliary chiral reagents, (*R*)- and (*S*)-PGME. Daniellic acid[15a] (Figure 9B) and oliveric acid[18]

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(Figure 9C) isolated from *Daniellia oliveri* possess the absolute configuration 4*R*, 5*S*, 9*R*, 10*S*. Thus, the chiral carbon centers of quesnoin (**1**) are identical to those of isoozic acid (**2**) of the genus *Hymenaea*. *Hymenaea courbaril* L and *Hymenaea oblongifolia* Huber are the representative species of the genus *Hymenaea* including 14 species from the viewpoint of chemical components.

$^{13}$C NMR *J* modulated spectra were recorded with a dichloromethane extract of fresh resin of modern *H. courbaril*, $[\alpha]^{D}_{20}$ −24.1° (*c* 1, $CH_2Cl_2$), and *H. oblongifolia*, $[\alpha]^{D}_{20}$ −22.4° (*c* 1, $CH_2Cl_2$). The spectrum of *H. courbaril* showed several carbonyl signals at $\delta$ 185, $\delta$ 179, and $\delta$ 171 (Figure 10A). In contrast, the spectrum of *H. oblongifolia* presented one major carbonyl signal at $\delta$ 185 (Figure 10B), similar to that of Oise amber (Figure 3A). In fact, up to 90% of the constituent of *H. oblongifolia* was isoozic acid (**2**). The vinyl carbon signals between $\delta$ 106 and $\delta$ 150 were lost by transformation to aliphatic carbons during polymerization. Hence, we propose that the tree corresponding to modern *H. oblongifolia* Huber, Fabaceae, subfamily of Caesalpiniaceae, might exude the resin that becomes Oise amber.

*H. oblongifolia* is currently distributed only in the Amazon rainforest.[16] The presence of the tropical tree corresponding to modern *H. oblongifolia* in the Paris basin (France) implies that there might have been a hot climate in this region during the early Eocene in agreement with previously described climatic optimum.[19] Moreover, Eurasian and South American continents united to Gondwanaland began to split apart 100 million years ago, and Eurasia and Africa drifted northward. The region corresponding to modern France could have been found in a geographically critical marshy zone belonging to Africa and a tropical zone 55 million years ago[19,20] and also be covered by rain forest extending through North Africa to the Amazon. Our finding is in accord with continental drift[21] caused by tectonic movement.[19]

The diversity of flora and fauna fossils of the Oise deposit as well as the contemporaneous London Clay may have been promoted by the climate optimum.[19] Recently, the analysis of arctic drilling disclosed that the climate of the North Pole was also subtropical 55 million years ago.[22] Quesnoin (**1**), a key organic compound aged 55 million years old and with an unusual novel skeleton, quesnane, allowed us to rank Oise amber as the oldest amber produced by an angiosperm corresponding to modern *H. oblongifolia*, which contributes to Earth's climate history.

## Experimental Section

**General Information.** $^{1}$H and $^{13}$C NMR spectra were recorded on 400 and 75 MHz spectrometers in $CDCl_3$. Chemical shifts were referenced to residual $CHCl_3$ $\delta_H$ 7.26 and $CDCl_3$ $\delta_C$ 77.0. NOESY spectra were recorded with a 1.5 s relaxation delay, 500 ms mixing time, and apodization with a shifted sine bell and baseline corrections.

**Material.** Oise amber were collected in 1997, at the Quesnoy locality in the Oise River area of the Paris basin (France) and dated by the Amber Group of Muséum National d'Histoire Naturelle. A voucher specimen was deposited in the Laboratoire d'Entomologie, Muséum National d'Histoire Naturelle. Baltic amber was provided by Laboratoire d'Entomologie and the two Hymenaea fresh resins by Prof. J. Saez (University of Antioquia).

**Isolation of Quesnoin (1).** Powdered Oise amber (25 g) was extracted with 3 × 100 mL of petroleum ether (yield 0.13 g) and 5 × 100 mL of $CH_2Cl_2$. The $CH_2Cl_2$ extracts (6.95 g) were separated into 24 fractions by chromatography on a silica gel column, by eluting with $CH_2Cl_2$−MeOH gradients. The combined factions 19−22 ($CH_2Cl_2$/MeOH, 93:7) were submitted to extensive chromatography. Further purification by TLC ($CH_2Cl_2$/MeOH, 93:7) was followed by RP-$C_{18}$ HPLC eluted by MeOH/$H_2O$ (60:40) to afford compound **1** (65 mg).

**Quesnoin (1). $C_{20}H_{30}O_4$.** Needles ($CHCl_3$−, 30% MeOH), mp 177 °C. $[\alpha]^{20}_{D}$ +5.3° (*c* 1.0, MeOH). HRESMS: *m*/*z* 335.2201 $[M + H]^+$ (335.2222 calcd for $C_{20}H_{31}O_4$). NMR data ($CDCl_3$) see Table 1 for $^{1}$H and $^{13}$C. ORTEP drawing of X-ray structure: ellipsoids were drawn at the 30% probability level (Figure 7). A CIF file was deposited at the Cambrige Crystallographic Data Centre, Structural Database accession number CCDC 628296 (S8−S10).

**Quesnoin-18-(*R*)-PGME Amide (1R).** Quesnoin (3.5 mg, 0.01 mmol), (*R*)-phenylglycine methyl ester (HCl) (2.5 mg, 0.013 mmol), PyBOP (6.5 mg, 0.013 mmol), and HOBT (1.7 mg, 0.013 mmol) were suspended in dry DMF (50 $\mu$L), and *N*-methylmorpholine (4 $\mu$L) was added at 0 °C with stirring. After 3 h of reaction at room temperature, the mixture was diluted with 5 mL of $CH_2Cl_2$ and washed with 4% HCl, followed by $H_2O$. The residue of the extract afforded the 18-(*R*)-PGME amide of **1** (**1R**) (2 mg) by purification on TLC ($CH_2Cl_2$/MeOH 95:5). $[\alpha]^{20}_{D}$ −18° (*c* 0.2, MeOH). HRESMS: *m*/*z* 482.2931 $[M + H]^+$ (482.2906 calcd for $C_{29}H_{40}NO_5$). $^{1}$H and $^{13}$C NMR ($CDCl_3$), see Table 1.

**Quesnoin-18-(*S*)-PGME Amide (1S).** Quesnoin (3.5 mg, 0.01 mmol) and (*S*)-phenylglycine methyl ester (HCl) (2.5 mg, 0.013 mmol) were treated in the same manner to give 2.5 mg of **1S**, $[\alpha]^{20}_{D}$ +37° (*c* 0.2, MeOH). HRESMS: *m*/*z* 482.2892 $[MH]^+$ (482.2906 calcd for $C_{29}H_{40}NO_5$). $^{1}$H and $^{13}$C NMR ($CDCl_3$), see Table 1.

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**Supporting Information Available:** $^{1}$H NMR spectra of **1**, **1R**, and **1S**; $^{13}$C NMR spectrum of **1**; HSQC and HMBC spectra of **1**; NOESY spectrum of **1**; crystal structure and analysis of **1**; CIF file for **1**·$H_2O$; and Table I. This material is available free of charge via the Internet at http://pubs.acs.org.

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