Sesquiterpenoids and Cytotoxic Lignans from the Bark of Libocedrus chevalieri

9 AUTHORS, INCLUDING:

Ying-Jun Zhang

Kunming Institute of Botany, CAS, Kunming, …

153 PUBLICATIONS **1,984** CITATIONS

SEE PROFILE

Marc Litaudon

French National Centre for Scientific Research

218 PUBLICATIONS **1,981** CITATIONS

SEE PROFILE

Stéphane Léonce

Servier

181 PUBLICATIONS **3,002** CITATIONS

SEE PROFILE

Françoise Guéritte

French National Centre for Scientific Research

222 PUBLICATIONS **4,961** CITATIONS

SEE PROFILE

Sesquiterpenoids and Cytotoxic Lignans from the Bark of *Libocedrus chevalieri*

Ying-Jun Zhang,[†,§] Marc Litaudon,*,[†] Hadjira Bousserouel,[†] Marie-Therese Martin,[†] Odile Thoison,[†] Stéphane Léonce,[‡] Vincent Dumontet,[†] Thierry Sévenet,[†] and Francoise Guéritte*,[†]

Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, 91198 Gif-sur-Yvette Cedex, France, and Institut de Recherche Servier, 125 Chemin de Ronde, 78290 Croissy-sur-Seine, France

Investigation of an EtOAc extract of the bark of *Libocedrus chevalieri* led to the isolation of a new cytotoxic lignan, 5-methoxy-4-epipodophyllotoxin (**1**), and three known podophyllotoxin analogues, 5-methoxypodophyllotoxin, 5-methoxypodophyllotoxin-4-*O*-β-D-glucoside, and podophyllotoxin-4-*O*-β-D-glucoside. Six sesquiterpenoids and a diterpenoid were also obtained. Of these, compounds **2**−**4** are new sesquiterpenoids, named libocedrines A−C, and 3β-hydroxyilicic alcohol was isolated for the first time from a higher plant. Structures of the new compounds were determined on the basis of spectroscopic methods. Cytotoxicity of the isolated compounds against KB and L1210 cells and their effects on tubulin assembly were evaluated.

The genus *Libocedrus* (Cupressaceae) contains 21 species native to North America, South America, and Western Pacific from New Zealand to China. It is sometimes placed in the segregate genus *Calocedrus* Kurz. Plants in the genus *Libocedrus* are monoecious or, rarely, dioecious evergreen trees or shrubs. The wood is reddish-brown or brown, soft, and moderately decay-resistant and has a spicy-resinous fragrance. Some species such as *L. decurrens* are important sources of timber. Two New Zealand species, *L. plumosa* and *L. bidwillii,* are also cultivated as ornamental plants. There are three endemic *Libocedrus* species, *L. austrocaledonica*, *L. yateensis*, and *L. chevalieri*, native to New Caledonia. Of them, *L. chevalieri* J. Buchholz is a bushy shrub 2−5 m in height, growing only on two mountaintops with ultramafic (ultrabasic) substrates. Lignans and terpenoids have been reported from *L. yateensis*, *L. plumosa*, and *L. bidwilli*;[1−3] however, no previous chemical work has been reported on *L. chevalieri*. In our hands, an EtOAc extract of the bark of *L. chevalieri* exhibited strong cytotoxicity against KB cells. Bioassay-guided purification of this extract by repeated column chromatography and semipreparative HPLC led to the isolation of new compounds (**1**−**4**) and a new isomer of 3-hydroxyilicic alcohol (**5**). Three known podophyllotoxin derivatives, 5-methoxypodophyllotoxin,[4−6] 5-methoxypodophyllotoxin-4-*O*-β-D-glucoside,[6,7] and podophyllotoxin-4-*O*-β-D-glucoside,[6] and two known terpenoids, 4α-hydroxy-4β-methyldihydrocostol[8−10] and *trans*-communic acid,[11] were identified by comparison of their spectroscopic data with reported literature values. The cytotoxicity of **1** and 5-methoxypodophyllotoxin against KB and L1210 cancer cells and tubulin assembly inhibitory activity are reported.

Compound **1** was assigned the molecular formula $C_{23}H_{24}O_9$ on the basis of the ^{13}C NMR data and positive ion HRESIMS. The ^1H and ^{13}C NMR spectra of **1** were closely related to those of 5-methoxypodophyllotoxin,[4−6] except for some differences observed at H-1/C-1 to H-4/C-4 and C-11. In the ^1H NMR spectrum of **1**, the small $J_{1,2}$ (4.9 Hz) and large $J_{2,3}$ (14.1 Hz) indicated the *cis* H-1/H-2 and *trans* H-2/H-3, which were the same as those of 5-methoxypodophyllotoxin, whereas the difference between the coupling constant $J_{3,4}$ (3.9 Hz for **1** and 8.1 Hz for 5-methoxypodophyllotoxin[4]) suggested the *cis* H-3/H-4 in **1**, indicating the presence of a 4β-OH. The ^1H and ^{13}C NMR spectra of **1** were also
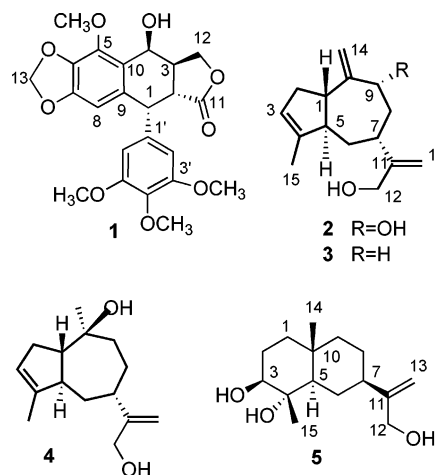
compared to those of 4-epipodophyllotoxin.[12] The main difference between the NMR spectra of **1** and 4-epipodophyllotoxin was the presence of a signal corresponding to a methoxy group at C-5 in **1** instead of a C−H aromatic signal in 4-epipodophyllotoxin. The configuration at C-4 was finally confirmed by the NOESY experiment, in which correlations of H-1 (δ 4.60) with H-2 (δ 3.26) and of H-3 (δ 2.75) with H-4 (δ 5.16) were observed. Therefore, compound **1** was determined to be 5-methoxy-4-epipodophyllotoxin.

Compound **2** was assigned as $C_{15}H_{22}O_2$ on the basis of the ^{13}C NMR and HRESIMS analysis. The ^{13}C NMR spectrum (Table 2) contained 15 carbon signals, consistent with two terminal olefinic carbons, four methylenes (including one oxygen-bearing carbon), four methines (including one oxygen-bearing carbon), and one methyl group. The partial structure $-C=C_{(3)}H-C_{(2)}H_2-C_{(1)}H-C_{(5)}H-C_{(6)}H_2-C_{(7)}H-C_{(8)}H_2-C_{(9)}HO-$ was deduced from ^1H (Table 1), ^{13}C, HMQC, and $^1H-^1H$ COSY spectra. In the HMBC spectrum of **2**, the terminal olefinic protons at δ 4.91, 5.17 (each s, H_2-14) were correlated with a quaternary olefinic carbon at δ 154.7 (C-10), a methine carbon at δ 46.4 (C-1), and the oxygen-bearing methine carbon at δ 76.2 (C-9). Terminal olefinic protons at δ 4.95 and 5.05 (each s, H-13) were correlated with a quaternary olefinic carbon at δ 154.8 (C-11), a methine carbon at δ 37.1 (C-7), and the oxygen-bearing methylene carbon at δ 64.8 (C-12). HMBC correlations of the singlet methyl proton at δ 1.61 (CH₃-15) with a methine carbon at δ 51.3 (C-5) and two olefinic carbons at δ 123.0 (C-3) and 141.5 (C-4) were also observed. The ROESY spectrum of **2** showed correlations of H-1 (δ 2.53) with H-6b (δ 1.57) and H-9 (δ 4.13) and of H-7 (δ 2.67) with H-9 and H-6b, revealing the *trans*-fused structure of **2**, in which H-1 had the same

---

* To whom correspondence should be addressed. Tel: +33-01-522-3235. Fax: +33-01-515-0124. E-mail: litaudon@icsn.cnrs-gif.fr; gueritte@icsn.cnrs-gif.fr.
† Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette.
‡ Institut de Recherche Servier, Croissy-sur-Seine.
§ Present address: Kunming Institute of Botany, Chinese Academy of Sciences, Heilongtan, Kunming 650204, China.

Table 1. ^{1}H NMR Spectroscopic Data (500 MHz) for Librocedrine A−C (**2**−**4**) and **5**

position	**2**[a]	**3**[a]	**4**[b]	**5**[b]
1a, 1b	2.53 m	2.65 q (9.2)	2.32 m	1.42 m 1.20 m
2a, 2b	2.56 m 2.29 dd (13.5, 5.0)	2.43 m 2.33 m	2.29 m 2.29 m	1.54 m 1.68 m
3	5.33 br s	5.35 s	5.28 br s	3.36 dd (11.9, 4.7)
5	2.51 m	2.50 m	2.48 m	1.25 m
6a, 6b	1.93 ddd (13.7, 9.1, 5.7) 1.57 dd (13.7, 7.0)	2.04 ddd (13.9, 6.7, 4.5) 1.45 ddd, (13.9, 11.8, 7.4)	1.96 ddd (13.5, 8.1, 5.3) 1.48 ddd (16.8, 12.0, 8.2)	1.93 m 1.27 m
7	2.67 bq (9.2)	2.59 btt (8.4, 5.9)	2.50 m	1.99 m
8a, 8b	1.98 bd (13.0) 1.87 bd (13.0)	1.76 m	1.64 m	1.59 m 1.47 m
9a, 9b	4.13 bd (10.2)	2.53 bdd, (9.7, 4.9) 2.22 m	1.90 ddd (13.2, 7.3, 1.5) 1.59 br dd (13.2, 7.5)	1.50 m 1.17 m
12	4.16 s	4.14 s	4.07 br s	4.06 s
13a	5.05 s	5.10 s	5.04 br s	5.02 s
13b	4.95 s	4.97 s	4.91 brs	4.90 s
14a	5.17 s	4.73 s	1.16 s	0.92 s
14b	4.91 s	4.66 s		
15	1.61 s	1.65 s	1.63 s	1.02 s

[a] Measured in CDCl$_3$. [b] Measured in CD$_3$OD.

Table 2. ^{13}C NMR and DEPT Data of Compounds **2**−**5**

position	**2**[a]	**3**[a]	**4**[b]	**5**[b]
1	46.4 d	50.7 d	55.6 d	40.5 t
2	33.7 t	34.3 t	34.0 t	28.9 t
3	123.0 d	123.3 d	123.8 d	80.5 d
4	141.5 s	142.0 s	143.2 s	76.5 s
5	51.3 d	49.8 d	47.0 d	54.3 d
6	36.2 t	36.6 t	37.9 t	27.6 t
7	37.1 d	40.0 d	42.3 d	43.2 d
8	40.4 t	29.8 t	27.7 t	28.5 t
9	76.2 d	37.6 t	46.8 t	45.8 t
10	154.7 s	152.6 s	75.3 s	35.6 s
11	154.8 s	154.0 s	156.7 s	155.4 s
12	64.8 t	65.1 t	65.0 t	65.3 t
13	108.3 t	108.5 t	108.0 t	107.9 t
14	102.9 t	106.6 t	22.2 q	19.3 q
15	14.6 q	14.9 q	14.9 q	16.5 t

[a] Measured in in CDCl$_3$. [b] Measured inCD$_3$OD.

orientation as H-7 and H-9. Therefore, the structure and relative configuration of **2** were determined. Compound **2** is a new sesquiterpenoid, 3,10(14),11(13)-guaiatriene-9,12-diol, and was named librocedrine A.

Compound **3** had the molecular formula C$_{15}$H$_{22}$O on the basis of its ^{13}C NMR data (Table 1) and its HRESIMS spectrum. The ^{1}H and ^{13}C NMR spectra of **3** (Tables 1 and 2) were closely related to those of **2**, except for obvious differences at C-8 (δ 29.8) and C-9 (δ 37.6). DEPT data of **3** indicated that C-9 was a methylene carbon, while that in **2** was an oxygen-bearing methine carbon. These observations suggested that **3** had no OH group attached at C-9. The structure of **3** was confirmed by its ^{1}H−^{1}H COSY, HMBC, and ROESY spectra as 3,10(14),11(13)-guaiatrien-12-ol and was named librocedrine B.

The molecular formula of **4** was deduced to be C$_{15}$H$_{24}$O$_2$ on the basis of the ^{13}C NMR, DEPT data, and HRESIMS analysis. The ^{1}H and ^{13}C NMR spectra of **4** (Tables 1 and 2) were similar to those of **3**, except for differences at C-10 (δ 75.3, s) and C-14 (δ 22.2, q). Instead of a carbon−carbon double bond between C-10 (δ 152.6, s) and C-14 (δ 106.6, t) as in **3**, compound **4** had an oxygen-bearing quaternary carbon and a methyl group attached to

C-10. The structure of **4** was confirmed by the ^{1}H−^{1}H COSY and HMBC spectra. In the ROESY spectrum of **4**, correlations of H-1 (δ 2.32) with H-6b (δ 1.48) and H-9b (δ 1.59), and H-7 (δ 2.50) with H-9b and H-6b, revealed the *trans*-fused structure of **4**, the same as in **2** and **3**. The positions of the methyl and OH groups at C-10 were evident from the ROESY correlations between CH$_3$-14 (δ 1.16) and H-5 (δ 2.48). Thus, the structure of compound **4** was determined as 3,11(13)-guaiadiene-10,12-diol, and it was named librocedrine C.

The HRESIMS spectrum of **5** corresponded to the molecular formula C$_{15}$H$_{26}$O$_3$. The ^{1}H and ^{13}C NMR data (Tables 1 and 2) were similar to those of 3β-hydroxyilicic acid[13] except for the presence in **5** of signals at δ 4.06 and 65.3 due to an allylic alcohol instead of a carboxylic acid. Thus, the structure of **5** was determined as 3β-hydroxyilicic alcohol (11(13)-eudesmene-3,4,12-triol) and confirmed from 2D experiments, ^{1}H−^{1}H COSY, HMQC, HMBC, and ROESY. 3β-Hydroxyilicic alcohol was obtained by bioconversion of ilicic alcohol with *Aspergillus niger* sp.[14] However, the chemical shift of carbon 11 at δ 96.1 in ref 14 is doubtful when compared with the one given for 3β-hydroxyilicic acid (δ 146.9),[13] for ilicic alcohol (δ 154.1),[15] and for compound **5** (δ 155.4). An [α]$^{25}_D$ value of −25 was measured for compound **5**. This value is in the range of values obtained for 3β-hydroxyilicic acid and analogues,[13] whereas an [α]$^{25}_D$ of +162 is mentioned for 3β-hydroxyilicic alcohol obtained from the bioconversion of ilicic alcohol with cultures of filamentous fungi.[14] These differences between compound **5** and 3β-hydroxyilicic alcohol described in ref 14 led us to suggest that the structure of the compound obtained by bioconversion is incorrect. This was the first time that 3β-hydroxyilicic alcohol had been isolated from a higher plant.

The compounds were evaluated for cytotoxicity against human epidermoid carcinoma KB cells, and docetaxel (KB cells, IC$_{50}$ at 2 × 10^{-10} M) was used as positive control. Only the new podophyllotoxin analogue (**1**) and 5-methoxypodophyllotoxin exhibited strong cytotoxicity on KB cells, with IC$_{50}$ values of 45 and 11 nM, respectively. Compound **1** exhibited an IC$_{50}$ of only 82 μM toward murine lymphocytic leukemia L1210 cells. The two compounds were also evaluated for their tubulin assembly inhibitory activity. Compound **1** inhibited the assembly of tubulin into microtubules with an IC$_{50}$ of 9 μM, whereas the IC$_{50}$ of 5-methoxypodophyllotoxin was 5 μM. 5-Methoxy-4-epipodophyllotoxin (**1**) is a new analogue of podophyllotoxin, a family of compounds whose antitumor activity has captured the attention of organic and medicinal chemists for many years. Several hundred podophyllotoxin analogues have been prepared, culminating with the clinical introduction of semisynthetic compounds such as etoposide,[16,17] teniposide,[18] and more recently etopophos.[19,20]

Experimental Section

General Experimental Procedures. Optical rotations were measured at 25 °C on a JASCO P1010 polarimeter. IR spectra were measured on a Nicolet FTIR 205 spectrophotometer. NMR spectra were recorded on a Bruker spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, and 600 MHz for 2D NMR) at 25 °C, using TMS as an internal standard. Chemical shifts (relative to TMS) are in ppm, and coupling constants (in parentheses) are in Hz. The 2D ROESY and NOESY spectra were recorded at mixing times of 500 and 600 ms, respectively. ESIMS spectra were obtained on a Navigator Mass Thermoquest. HRESIMS were obtained on a MALDI-TOF spectrometer (Voyager-De STR; Perspective Biosystems). HPLC was performed using a Waters Autopurification system equipped with a UV−vis diode array detector (190−600 nm) and a Pl-ELS 1000 ELSD detector (Polymer Laboratory). Precoated silica gel plates (Merck) were used for TLC. Detection was done by spraying plates with 5% anisaldehyde-sulfuric acid, followed by heating.

Plant Material. Bark of *Libocedrus chevalieri* was collected in September 2002 in the high altitude scrubland of Humboldt, South Province, New Caledonia, by one of us (V.D.). A voucher specimen

(DUM-0188) is deposited in the Herbarium of the Botanical and Tropical Ecology Department of the IRD Center, Noumea, New Caledonia.

Cytotoxicity Activity and Tubulin Assay. The human tumor cell lines KB (mouth epidermoid carcinoma) and L1210 (murine lymphocytic cells) were originally obtained from the ATCC. The cytotoxicity assays were performed according to published procedures.[21,22] Inhibition of tubulin assembly was determined according to Zavala and Guenard's method.[23]

Extraction and Isolation. The powdered, air-dried bark of *L. chevalieri* (100 g) was extracted three times with EtOAc at room temperature to afford an EtOAc extract (14.2 g), which displayed a significant inhibitory activity on KB cells (85% inhibition with a concentration of 10 μg/mL). The EtOAc extract (14 g) was subjected to flash column chromatography on C_{18} eluting with CH_3CN-H_2O (30%−100%) to give nine fractions (1−9). Fractions 1 and 2 were found to be the most cytotoxic, inhibiting KB cell growth by 95% at 10 μg/mL. Fraction 1 (6.5 g) was subjected to flash column chromatography on VersaPak C_{18} (MeOH−H_2O, 20%−100%), silica gel ($CHCl_3$−MeOH, 1:0−4:1), and preparative HPLC to yield **5** (8.6 mg), 5-methoxypodophyllotoxin 4-*O*-β-D-glucoside (94 mg), and podophyllotoxin 4-*O*-β-D-glucoside (1.3 mg). Fractions 2 (1.1 g) and 5 (712 mg) were separately chromatographed over silica gel eluting with heptane−EtOAc (1:0−0:1). Then semipreparative HPLC using a Kromasil-R C_{18} column (250 × 46 mm, 5 μm) with a gradient mobile phase consisting of acetonitrile−water (50:50−80:20) afforded **1** (12.8 mg), **2** (78.4 mg), and **4** (6.2 mg) from fraction 2 and **3** (67.8 mg) from fraction 5. Column chromatography of fractions 3 (1.0 g) and 4 (461 mg) on silica gel eluting with heptane−EtOAc (1:0−1:1) furnished **2** (27.4 mg), 5-methoxypodophyllotoxin (31.5 mg), and 4α-hydroxy-4β-methyldihydrocostol (106.3 mg) from fraction 3 and *trans*-communic acid (28.6 mg) from fraction 4.

5-Methoxy-4-epipodophyllotoxin (1): yellowish, amorphous powder; $[\alpha]^{25}_D$ −29.0 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.33 (2H, s, H-2',6'), 6.29 (1H, s, H-8), 5.95 (2H, s, H-13), 5.16 (1H, d, *J* = 3.9 Hz, H-4), 4.60 (1H, d, *J* = 4.9 Hz, H-1), 4.48 (1H, dd, *J* = 9.3, 8.6 Hz, H-12a), 4.34 (1H, dd, *J* = 8.2, 8.0 Hz, H-12b), 4.17 (3H, s, 5-OMe), 3.82 (3H, s, 4'-OMe), 3.79 (6H, s, 3', 5'-OMe), 3.26 (1H, dd, *J* = 14.1, 4.9 Hz, H-2), 2.75 (1H, m, H-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.2 (C-11), 152.6 (C-3',5'), 149.9 (C-7), 141.1 (C-5), 137.4 (C-4'), 135.1 (C-1'), 134.6 (C-6), 132.8 (C-9), 124.4 (C-10), 108.5 (C-2',6'), 104.4 (C-8), 101.3 (C-13), 67.4 (C-12), 62.1 (4'-OMe), 61.6 (C-4), 59.8 (5-OMe), 56.4 (3', 5'-OMe), 44.1 (C-2), 41.0 (C-1), 37.5 (C-3); ESIMS (positive mode) *m/z* 467.1 [M($C_{23}H_{24}O_9$) + Na]$^+$; HRESIMS *m/z* 467.1307 [M + Na]$^+$ (calcd for $C_{23}H_{24}O_9Na$ 467.1318).

Libocedrine A (2): colorless oil; $[\alpha]^{25}_D$ +158.0 (*c* 0.8, $CHCl_3$); IR ν_{max} 3360, 2923, 2855, 1700, 1645, 1448, 1042, 897, 800, 668 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 2; ESIMS (positive mode) *m/z* 257.2 [M($C_{15}H_{22}O_2$) + Na]$^+$; HRESIMS *m/z* 257.1450 [M + Na]$^+$ (calcd for $C_{15}H_{22}O_2Na$ 257.1517).

Libocedrine B (3): colorless oil; $[\alpha]^{25}_D$ +110.0 (*c* 1.05, $CHCl_3$); IR ν_{max} 3315, 2921, 2852, 1635, 1437, 1020, 884, 801, 723 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 2; ESIMS (positive mode) *m/z* 219 [M($C_{15}H_{22}O$) + H]$^+$; HRESIMS *m/z* 219.1736 [M + H]$^+$ (calcd for $C_{15}H_{23}O$, 219.1749).

Libocedrine C (4): colorless oil; $[\alpha]^{25}_D$ +38.0 (*c* 0.24, $CHCl_3$); IR ν_{max} 3340, 2920, 2852, 1456, 1376, 1053, 801, 760, 721, 668 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 2; ESIMS (positive mode) *m/z* 219.2 [M($C_{15}H_{24}O_2$) + H − H_2O]$^+$; HRESIMS *m/z* 219.1787 [M + H − H_2O]$^+$ (calcd for $C_{15}H_{23}O$, 219.1787).

Compound 5: amorphous powder; $[\alpha]^{25}_D$ −25.0 (*c* 0.12, EtOH); IR ν_{max} 3346, 2925, 2852, 1651, 1456, 1382, 1164, 1078, 1032, 929, 903, 668 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 277.1 [M($C_{15}H_{26}O_3$) + Na]$^+$; HRESIMS *m/z* 277.1773 [M + Na]$^+$, calcd 277.1780 for $C_{15}H_{26}O_3Na$.

References and Notes

(1) Erdtman, H.; Harmatha, J. *Phytochemistry* **1979**, *18*, 1495−1500.
(2) Perry, N. B.; Foster, L. M. *Phytomedicine* **1994**, *1*, 233−237.
(3) Russell, G. B. *Phytochemistry* **1975**, *14*, 2708.
(4) Van Uden, W.; Homan, B.; Woerdenbag, H. J.; Pras, N.; Malingre, T. M.; Wichers, H. J.; Harkes, M. *J. Nat. Prod.* **1992**, *55*, 102−110.
(5) Feliciano, A. S.; Miguel del Corral, J. M.; Gordaliza, M.; Castro, A. *Phytochemistry* **1990**, *29*, 1335−1338.
(6) Broomhead, A. J.; Dewick, P. M. *Phytochemistry* **1990**, *29*, 3839−3844.
(7) Berlin, J.; Bedorf, N.; Mollenschott, C.; Wray, V.; Sasse, F.; Hofle, G. *Planta Med.* **1988**, *54*, 204−206.
(8) Gonzalez, A. G.; Barrera, J. B.; Mendez, J. T.; Sanchez, M. L.; Martinez, J. L. E. *Phytochemistry* **1992**, *31*, 1816−1817.
(9) Guerreiro, E.; Kavka, J.; Giordano, O. S.; Gros, E. G. *Phytochemistry* **1979**, *18*, 1235−1237.
(10) Ahmed, A. A.; Mahmoud, A. A. *Tetrahedron* **1998**, *54*, 8141−8152.
(11) Muhammad, I.; Mossa Jaber, S.; Al-Yahya Mohammed, A.; Ramadan Ahmed, F.; El-Feraly Farouk, S. *Phytother. Res.* **1995**, *9*, 584−588.
(12) Engelherdt, U.; Sarkar, A.; Linker, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2487−2489.
(13) Abu Zarga, M. H.; Hamed, E. M.; Sabri, S. S.; Voelter, W.; Zeller, K.-P. *J. Nat. Prod.* **1998**, *61*, 798−800.
(14) Carrizo, R.; Pous, L.; Sanz, M. K.; Ardanaz, C.; Guerreriro, E. *Nat. Prod. Lett.* **2002**, *16*, 9−14.
(15) Gonzalez, A. G.; Barrera, J. B.; Mendez, J. T.; Sanchez, M. L.; Martinez, J. L. E. *Phytochemistry*, **1992**, *31*, 1816−1817.
(16) Stahelin, H. *Eur. J. Cancer* **1973**, *9*, 215−221.
(17) Hande, K. R. *Eur. J. Cancer* **1998**, *34*, 1514−1521.
(18) Stahelin, H. *Eur. J. Cancer* **1970**, *6*, 303−311.
(19) Schacter, L. *Semin. Oncol.* **1996**, *23*, 1−7.
(20) Witterland, A. H.; Koks, C. H.; Beijinen, J. H. *Pharm. World Sci.* **1996**, *18*, 163−170.
(21) Da Silva, A. D.; Machado, A. S.; Tempête, C.; Robert-Gero, M. *Eur. J. Med. Chem.* **1994**, *29*, 149−152.
(22) Pierré, A.; Kraus-Berthier, L.; Atassi, G.; Cros, S.; Poupon, M. F.; Lavielle, G.; Berlion, M.; Bizzari, J. P. *Cancer Res.* **1991**, *51*, 2312−2318.
(23) Zavala, F.; Guénard, D.; Robin, J.-P.; Brown, E. *J. Med. Chem.* **1980**, *23*, 546−549.