Sesquiterpenoid Constituents of *Meriandra benghalensis* (Labiatae). X-ray Structure Analysis

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Received March 4, 1983

The eudesmanes benghalensin A (1) and B (2) and the cadinane derivative benghalensitriol (3) have been isolated from the acetone extract of *Meriandra benghalensis*. The structures and absolute configurations of the three sesquiterpenoids have been elucidated by X-ray analysis of the natural compounds. Chemical and spectroscopic methods have also been used.

In continuation of our work on terpenic compounds from Labiatae, we have now investigated a *Meriandra* species, a genus botanically close to *Salvia*.[2-5] *Meriandra benghalensis* (Roxb.) Benth. (Labiatae) is widespread in Abyssinia and has been in local use as an aromatic, culinary herb. The essential oil of this plant is rich[6] in camphor, and the material of our study originates from plants cultivated since 1925 in the Botanical Garden, University of Palermo. Extraction of leaves and flowers with acetone afforded, after careful purification, ursolic and oleanolic acids, 2α,3α-dihydroxyurs-12-en-28-oic acid,[7] 2α,3α-dihydroxyolean-12-en-28-oic acid,[8] 2α,3β-dihydroxyurs-12-en-28-oic acid,[9] 2α,3β-dihydroxyolean-12-en-28-oic acid,[10] 5,4′-dihydroxy-3,6,7-trimethoxyflavone (penduletin),[11] and three new sesquiterpenoids: the eudesmanes benghalensin A (1) and B (2) and the cadinane derivative benghalensitriol (3), whose structures were established as follows.

Combustion analysis and mass spectrometry indicated the molecular formula $C_{15}H_{20}O_4$ for benghalensin A (1). Its IR spectrum was consistent with the presence of an hydroxyl group (3400 cm^{-1}) and an α,β,α′,β′ dienone (1657, 1629, 1608 cm^{-1}). In agreement with this hypothesis, the UV spectrum of 1 showed strong absorption at λ_{max} 242 nm (ε 14 000). The ^1H NMR spectrum of this compound showed signals for two secondary methyl groups at δ 0.97 and 1.07 (J = 7 Hz) which were assigned to an isopropyl group, a tertiary methyl group at δ 1.48, a two proton singlet at δ 4.81 which was assigned to a (C)–CH_2–O grouping, and signals for a cis-disubstituted olefin at δ 6.19 and 6.81 (J = 10 Hz), which must be conjugated with the ketone group. In confirmation of the above assignment, irradiation at δ 6.19 removed the 10-Hz coupling from the signal at δ 6.81.

The ^{13}C NMR spectrum of benghalensin A (see Table I) showed signals arising from three methyl groups, two methylene carbons, a methylene carbon bonded to an oxygen atom, two methine carbons, four olefinic carbons which were assigned to tetrasubstituted and disubstituted olefins, a quaternary carbon atom, an acetal carbon, and an α,β,α′,β′ dieneone.

Table I. ^{13}C NMR Chemical Shifts of Compounds 1-3[a]

atom	1	2	3
C1	157.5 d[b]	157.5 d	20.4 t
C2	125.2 d	127.3 d	34.9 t
C3	184.9 s	183.7 s	85.9 s
C4	129.9 s	133.2 s	45.8 t
C5	154.7 s	159.8 s	71.2 s
C6	98.7 s	112.6 s	46.9 d[c]
C7	49.5 d	75.7 s	20.4 t
C8	18.6 t	28.1 t	43.2 t
C9	36.5 t	32.0 t	76.7 s
C10	39.5 s	39.6 s	53.1 d[c]
C11	26.3 d	32.1 d	25.5 d
C12	23.4 q[c]	21.7 q[c]	24.0 q
C13	24.5 q[c]	18.0 q[c]	23.5 q
C14	19.3 q	17.5 q[c]	19.2 q
C15	68.9 t	71.8 t	99.4 d

[a] In pyridine-d_5 solution. Shifts are given in parts per million from Me_4Si. [b] SFORD multiplicity. [c] These assignments may be reversed, but those given here are considered to be the most likely.

All the above data may be accommodated by an eudesmane structure such as 1 for benghalensin A, in which the unusual endoperoxide 1,2-dioxane ring was established by molecular formula requirements.

The related isomeric structure 2 has been assigned to benghalensin B ($C_{15}H_{20}O_4$). Its spectral data (^1H NMR, UV, IR) were similar (see Experimental Section) to those of benghalensin A (1). The presence in benghalensin B (2) of a hydroxyl group at C7 and a C15–C6 hemiacetal instead of the endoperoxide bridge between C15 and C6 of compound 1 were established by comparison of the ^{13}C NMR data of these two compounds (see Table I). In the spectrum of 2 a doublet at 49.5 ppm associated with C7 has been replaced by a singlet at 75.7 ppm. In addition, the differences observed in the δ_C values of some of the carbon atoms (C6, C8, C9, and C11) of compounds 1 and 2 reflected their structural difference at C7.

The third new sesquiterpenoid isolated from *M. benghalensis*, benghalensitriol (3), had a molecular formula of $C_{15}H_{26}O_4$, and its IR spectrum showed hydroxyl absorptions (3480, 3330 cm^{-1}). Its ^1H NMR spectrum showed signals for a tertiary methyl group at δ 1.45 and an isopropyl group at δ 0.82 and 1.08 (d, J = 7 Hz). In addition, the ^1H NMR spectrum of benghalensitriol (3) showed a one-proton singlet at δ 5.19, which was assigned to a hemiacetal functionality placed on a carbon without vicinal protons.

Ac_2O–pyridine treatment of 3 gave a diacetate ($C_{19}H_{30}O_6$, 4; ν_{OH} 3270 cm^{-1}), the ^1H NMR spectrum of which showed

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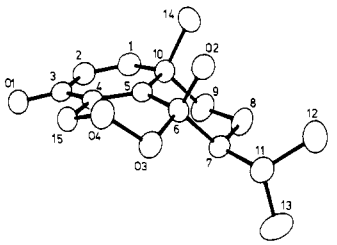


Figure 1. Perspective drawing of molecule 1 showing its absolute configuration. Thermal ellipsoids at the 50% of probability.

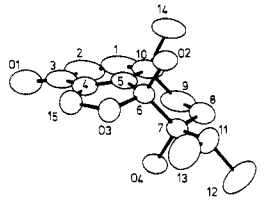


Figure 2. Perspective drawing of molecule 2 showing its absolute configuration. Thermal ellipsoids at the 50% of probability.

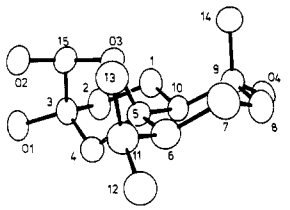
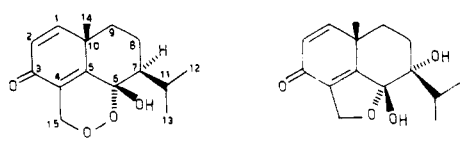


Figure 3. Perspective drawing of molecule 3 showing its absolute configuration. Thermal ellipsoids at the 50% of probability.

the hemiacetal proton shifted to δ 6.37. CrO_3–pyridine treatment of the natural substance (**3**) gave a compound (**5**, $C_{15}H_{24}O_4$) which possessed a γ-lactone group (ν_{CO} 1785 cm^{-1}) instead of the hemiacetal function found in **3**. Evidence for this is the fact that the ^1H NMR spectrum of this derivative (**5**) lacked the signal assigned to the hemiacetal proton.

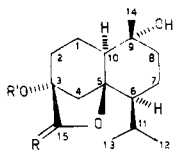
Finally, the ^{13}C NMR spectrum (Table I) of benghalensitriol (**3**) was in agreement with all the above deductions; it contained signals for three methyl groups, five methylene carbons, three methine carbons, one hemiacetal carbon (doublet at 99.4 ppm), and three downfield quaternary carbon atoms (singlets at 85.9, 76.7, and 71.2 ppm). Whereas it is difficult to accommodate these spectral data on an eudesmane skeleton, they may be accommodated readily as a cadinane sesquiterpene, **3**.

Single crystal X-ray analyses of the three new sesquiterpenoids were undertaken in order to confirm the proposed structures, to establish their stereochemistry, and to determine the absolute configurations of compounds **1–3**. Figures 1–3 are perspective views[12] of the molecules



1

2



3, R = β H, α OH ; R' = H

4, R = β H, α OAc ; R' = Ac

5, R = O , R' = H

Table II. Some Torsional Angles for the Three Compounds

	angle, deg (elsd)		
atoms[a]	1	2	3
1-2-3-4	0.1 (4)	−4.1 (7)	−59.5 (3)
2-3-4-5	−3.4 (4)	5.5 (6)	73.2 (3)
3-4-5-10	5.4 (4)	−2.3 (5)	−73.8 (3)
4-5-10-1	−4.0 (4)	−2.4 (5)	61.8 (3)
5-10-1-2	0.7 (4)	3.9 (6)	−45.6 (3)
10-1-2-3	1.0 (5)	−0.7 (9)	44.0 (4)
5-4-15-O4	15.7 (4)		
4-15-O4-O3	−57.7 (2)		
15-O4-O3-6	81.3 (2)		
O4-O3-6-5	−55.5 (2)		
O3-6-5-4	12.1 (4)		
6-5-4-15	8.7 (4)		
5-4-15-O3		−5.3 (4)	
4-15-O3-6		6.9 (3)	
15-O3-6-5		−5.8 (3)	
O3-6-5-4		2.4 (3)	
6-5-4-15		1.8 (4)	
5-4-3-15			−43.9 (3)
4-3-15-O3			33.6 (3)
3-15-O3-5			−8.6 (3)
15-O3-5-4			−19.4 (3)
O3-5-4-3			39.5 (3)
9-10-5-6	51.6 (3)	48.9 (4)	−43.2 (4)
10-5-6-7	−51.6 (3)	−50.9 (4)	45.3 (4)
5-6-7-8	51.3 (3)	46.6 (3)	−54.5 (4)
6-7-8-9	−57.3 (3)	−53.4 (4)	62.4 (4)
7-8-9-10	59.0 (3)	56.5 (4)	−57.6 (4)
8-9-10-5	−53.2 (3)	−47.7 (4)	47.6 (3)

[a] Carbon atoms unless indicated otherwise.

Table III. Conformational Parameters of Molecular Rings[a]

ring	compd	θ	Φ	q
A	3	160	7	0.67
B	1	6	314	0.56
	2	6	297	0.51
	3	168	100	0.54
C	1	56	208	0.63
	2		274	0.06
	3		227	0.45

[a] Ring A = C1, C2, C3, C4, C5, C10; ring B = C9, C10, C5, C6, C7, C8; ring C = C5, C4, C15, O4, O3, C6 for 1, C5, C4, C15, O3, C6 for 2, and C5, C4, C3, C15, O3 for 3. The parameters are the out of chair θ (in degrees), the pseudorotation Φ (in degrees), and the total amplitude q (in angstroms).

showing their absolute configurations. Tables II and III list the torsional angles and the conformational parameters[13] of the ring. The crystal packing is mainly due to the following intermolecular hydrogen bonds. Compound 1: O2–H···O1 (0.5 − x, 1 − y, 0.5 + z) = 2.928 (3) Å. Compound 2: O2–H···O4(1.5 − y, 0.5 + x, −0.25 + z) = 2.798 (3) Å, O4–H···O1 (−0.5 + x, 1.5 − y, 1.25 − z) = 2.877 (4) Å, and O4–H···O3 (x, y, z) = 2.734 (3) Å (bifurcated). Compound 3: O2–H···O1 (1 − y, x − y, −0.67 + z) = 2.743 (3) Å and O4–H···O4 (1 − y, −1 + x − y, 0.33 + z) = 2.771 (3) Å.

Experimental Section

Melting points were determined in a Kolfer apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter with a 1-dm cell. Elemental analyses were carried out in Madrid[1c] with the help of a Perkin-Elmer 240 analyzer.

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UV spectra were determinated on a Perkin-Elmer 402 recording spectrophotometer and IR spectra on a Perkin-Elmer 257 spectometer. ^1H and ^{13}C NMR were measured at 90 and 25.2 MHz, respectively, in $CDCl_3$ or pyridine-d_5 solution with Me_4Si as an internal standard. Mass spectra were obtained on a JEOL J-MS-01SG-2 instrument or on a Hitachi Perkin-Elmer RMU-6MG apparatus. Thin-layer chromatography was carried out on commercially preparated TLC plates (Merck). Column chromatography was carried out on silica gel (Kiesegel 60, 70–230 mesh, ASTM) supplied by Merck.

Extraction of *Meriandra benghalensis*. The plant was collected and identified in the Botanic Gardens, Palermo. Air-dried and powdered material (0.6 kg) was extracted with acetone at room temperature for 1 week. After filtration, the solvent was evaporated to give a gum which was subjected to dry column chromatography on silica gel (deactivated with 15% water). Elution with petroleum ether gave alkanes, fats, and waxes which were rejected. Elution with petroleum ether–ethyl acetate mixtures yielded the following compounds in order of elution: benghalensin A (**1**, 300 mg), ursolic and oleanolic acid mixture (7.5 g), 2α,3α-dihydroxyurs-12-en-28-oic and 2α,3α-dihydroxyolean-12-en-28-oic acid mixture (80 mg), benghalensin B (**2**, 40 mg), 5,4′-dihydroxy-3,6,7-trimethoxyflavone (penduletin, 300 mg), 2α,3β-dihydroxyurs-12-en-28-oic and 2α,3β-dihydroxyolean-12-en-28-oic acid mixture (200 mg), benghalensitriol (**3**, 60 mg). The previously known compounds were identified by their physical (melting point, $[\alpha]_D$) and spectroscopic (IR, UV, ^1H NMR, MS) data and by comparison with authentic samples.

Benghalensin A (1): mp 123 °C (from EtOAc–petroleum ether); $[\alpha]_D^{22}$ −311 ° (*c* 0.441, $CHCl_3$); IR (*nujol*) ν_{max} 3400, 1657, 1629, 1608 cm^{-1}; UV (EtOH) λ_{max} 242 nm (ε 14 000); ^1H NMR ($CDCl_3$) δ 6.81 (1 H, d, *J* = 10 Hz, H-1), 6.19 (1 H, d, *J* = 10 Hz, H-2), 4.81 (2 H, s, H-15), 1.48 (3 H, s, H-14), 1.07 and 0.97 (3 H each, d, *J* = 7 Hz, H-12 and H-13); ^{13}C NMR, see Table I; EIMS (direct inlet, 75 eV), *m/z* (relative intensity) 264 (M^+, 2), 248 (5), 246 (12), 232 (66), 231 (72), 217 (48), 203 (78), 189 (100), 177 (54), 163 (54), 149 (36), 135 (42), 121 (30), 115 (18), 106 (21), 91 (40), 77 (48), 55 (54), 41 (84). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.45; H, 7.80.

Benghalensin B (2): mp 163 °C (from EtOAc–petroleum ether); $[\alpha]^{22}_D$ −114.5° (*c* 0.131 $CHCl_3$); IR (KBr) ν_{max} 3470, 3310, 1682, 1642, 1600 cm^{-1}; UV (EtOH) λ_{max} 241 nm (ε 9000); ^1H NMR ($CDCl_3$) δ 6.88 (1 H, d, *J* = 10 Hz, H-1), 6.22 (1 H, d, *J* = 10 Hz, H-2), 5.02 and 4.71 (AB system, *J* = 13 Hz, 2 H, H-15), 1.41 (3 H, s, H-14), 1.09 and 0.98 (3 H each, d, *J* = 7 Hz, H-12 and H-13); ^{13}C NMR, see Table I; EIMS (direct inlet, 75 eV), *m/z* (relative intensity) 264 (M^+, 1), 249 (6), 246 (1), 231 (2), 203 (4), 175 (3), 165 (100), 147 (20), 135 (4), 119 (6), 100 (8) 91 (5), 71 (8), 55 (5). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.95; H, 7.75.

Benghalensitriol (3): mp 218 °C (from EtOAc); $[\alpha]_D^{22}$ +7.9° (*c* 0.126, pyridine); IR (Nujol) ν_{max} 3480, 3330 cm^{-1}; ^1H NMR (pyridine) δ 5.19 (1 H, s,, H-15), 1.45 (3 H, s, H-14 protons), 1.08 and 0.82 (3 H each, d, *J* = 7 Hz, H-12 and H-13); ^{13}C NMR, see Table I; EIMS (direct inlet, 75 eV), *m/z* (relative intensity) M^+ absent, 255 (M^+ − 15, 1), 252 (2), 237 (3), 224 (11), 206 (21), 191 (8), 188(5), 163 (18), 148 (18), 145 (18), 141 (18), 139 (88), 123(41), 105 (18), 97 (50), 81 (18), 71 (33), 58 (30), 43 (100). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.52; H, 9.92.

Compound 4. A solution of 25 mg of crude benghalensitriol (**3**) in 2 mL of pyridine and 0.5 mL of acetic anhydride was allowed to stand overnight at room temperature. The reaction mixture was poured into ice–water and extracted with EtOAc. The EtOAc layer was washed with water, dried, and evaporated. The crude product was purified by column chromatography on silica gel. Elution with petroleum ether–EtOAc (1:1) gave 20 mg of **4**: mp 108 °C (from EtOAc–petroleum ether); $[\alpha]_D^{22}$ +35.2° (*c* 0.156, $CHCl_3$); IR (Nujol) ν_{max} 3270, 1740, 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37 (1 H, s, H-15), 2.0 (6 H, s, $2COCH_3$); 1.21 (3 H, s, H-14), 0.95 and 0.81 (3 H each, d, *J* = 7 Hz, H-12 and H-13); EIMS (direct inlet, 75 eV), *m/z* (relative intensity) 354 (M^+, 1), 295 (5), 294 (5), 234 (45), 224 (55), 216 (72), 206 (41), 191 (40), 173 (100), 145 (54), 139 (72), 123 (45), 105 (45), 97 (50), 69 (60). Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.64; H, 8.70.

Compound 5. Benghalensitriol (**3**, 20 mg) was added to a solution of CrO_3 (50 mg) in pyridine (5 mL), and the mixture was stirred overnight at room temperature. Dilution with water and extraction with EtOAc yielded crude **5**, which was purified by silica gel column chromatography, by elution with petroleum ether–EtOAc (1:1), to yield 15 mg of pure **5**: mp 163 °C (from EtOAc); $[\alpha]_D^{28}$ −46.9° (*c* 0.196, pyridine); IR (KBr) ν_{max} 3510, 3440, 3230, 1760 cm^{-1}; ^1H NMR (pyridine) δ 1.42 (3 H, s, H-14), 0.89 and 0.85 (3 H each, d, *J* = 7 Hz, H-12 and H-13); EIMS (direct inlet, 75 eV), *m/z* (relative intensity) 268 (M^+, 1), 253 (4), 250 (10), 235 (4), 232 (64), 224 (30), 206 (43), 189 (48), 163 (18), 139 (100), 123 (56), 97 (60), 71 (43), 43 (90). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.16; H, 8.95. Found: C, 67.42; H, 9.04.

Table IV. Crystal Data

parameter	1	2	3
chemical formula	$C_{15}H_{20}O_4$	$C_{15}H_{20}O_4$	$C_{15}H_{32}O_4$
latice type	orthorhombic, $P2_12_12_1$	tetragonal, $P4_32_12$	trigonal, $P3_1$
a, Å	14.402 (2)	11.488 (1)	14.650 (1)
b, Å	13.055 (2)	11.488 (1)	14.650 (1)
c, Å	7.218 (1)	22.588 (1)	6.168 (1)
z	4	8	3
mol wt, g mol^{-1}	264.32	264.32	276.42
d_c, g cm^{-3}	1.29	1.18	1.20
μ (CuK), cm^{-1}	7.21	6.57	6.43
crystal size	0.2 × 0.3 × 0.3	0.3 × 0.2 × 0.2	0.1 × 0.2 × 0.3
no. of independent Friedel pairs:	1353	1535	1305

X-ray Structure Determination of 1–3. Table IV shows some crystal data of the three compounds. All data were collected on a four-circle diffractometer. Graphite-monochromated Cu Kα radiation (λ = 1.541 78 Å), the $\omega/2\theta$ scan technique, and a scan speed of 1°/min were used. No crystal decompositions were observed during the data collection processes. No absorption corrections were applied. After correction for Lorentz and polarization factors, 1277 (compound **1**), 1080 (compound **2**) and 1223 (compound **3**), Friedel pairs were considered as observed with the criterion $I > 2\sigma(I)$ and were used in the remaining calculations. Scattering factors for neutral atoms and anomalous dispersion corrections for O and C atoms were taken from the literature.[14] The three crystal structures were solved by using the program MULTAN.[15] Most of remaining calculations were performed with the X-RAY 70 system.[16] The structures were first refined anisotropically with unit weights. The H atoms were located on difference maps calculated with those reflexions within $\sin\theta/\lambda < 0.5$ Å^{-1}. Convenient weighting schemes were chosen[17] to obtain flat dependence of $\langle w\Delta^2F \rangle$ vs. $\langle F_o \rangle$ and vs. $\langle \sin\theta/\lambda \rangle$. Several cycles of weighted anisotropic refinement (fixed contribution of H atoms, except in compound **1** where H coordinates were allowed to vary) gave the following unweighted and weighted discrepancy indices: $R = 0.042$, $R_w = 0.046$, compound **1**; $R = 0.048$, $R_w = 0.061$, compound **2**; $R = 0.046$, $R_w = 0.058$, compound **3**. The absolute configurations of the three compounds were determined by comparing the 96 ($\Delta F_c > 0.07$, compound **1**), 29 ($\Delta F_c > 0.10$, compound **2**), and 80 ($|\Delta F_c| > 0.06$, compound **3**) more relevant Bijvoet pairs, giving the following average Bijvoet differences[18]: 0.371 (vs. 0.421 for reverse enantiomer of compound **1**), 0.376 (vs. 0.447 for compound **2**), 0.185 (vs. 0.250 for compound **3**).

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Acknowledgment. We thank Prof. F. Bruno, Botanical Garden, University of Palermo, for collection and botanical classification of the plant material. We also thank Prof. S. Garcia-Blanco (CSIC) for facilities given in the use of the four-circle diffractometer and the staff of the Centro de Proceso de Datos del Ministerio de Educatiôn, Madrid, for the use of the UNIVAC 1108 computer. This work was supported in part by a grant of "Progetto Finalizzato per la Chimica Fine e Secondaria" (CNR, Rome) and in part by the "Comisiôn Asesora de Investigacion Cientifica y Tēcnica" (Grant No. 11/81), Madrid. The financial support of the Spanish Foreign Ministry for travel facilities between Italy and Spain is greatefully acknowledged.

Registry No. 1, 87174-91-2; 2, 87174-92-3; 3, 87174-93-4; 4, 87174-94-5; 5, 87174-95-6.

Supplementary Material Available: Listings of atomic coordinates, anisotropic thermal parameters, bond lengths, and bond angles (12 pages). Ordering information is given on any current masthead page.

Studies in Cephalotaxus Alkaloids. Stereospecific Total Synthesis of Homoharringtonine

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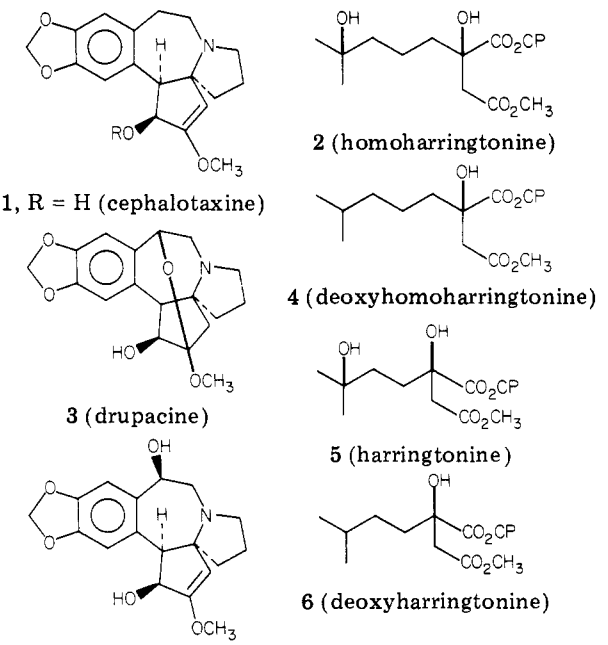
Received May 2, 1983

The alkaloid ester homoharringtonine (**2**) was synthesized stereospecifically via the Reformatsky reaction of methyl α-bromoacetate with cephalotaxyl pyruvate (**16**) obtained by esterification of cephalotaxine with acid chloride derived from **15**. The preparations of **2** and its unsaturated derivative **13** are described in detail. Possible explanations of the steric requirements in the esterification of cephalotaxine and of the steric outcome of the Reformatsky reaction leading to **2** and **13** are advanced.

Introduction

During the last decade the esters of the unusual homoerythrina alkaloid cephalotaxine (**1**, Chart I) have been scrutinized not only by the medical profession searching for antitumor activities but also by the community of synthetic chemists attracted by the unique structures of these alkaloids. Following their isolation from various species of *Cephalotaxus* native to Japan and China, most notably from the evergreen bush *Cephalotaxus harringtonia* and *Cephalotaxus drupacea* and *Cephalotaxus fortunei*,[2] the alkaloids have been subjected to a number of structural,[3] biosynthetic,[4] and synthetic studies.[5,6]

Chart I[a]



[a] CP = cephalotaxyl.

Some of the cephalotaxine esters have been prepared from the parent alkaloid by sequential esterification: the

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