Semisynthesis of Rosmanol and Its Derivatives. Easy Access to Abietatriene Diterpenes Isolated from the Genus *Salvia* with Biological Activities

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Received November 9, 2001

The known diterpenes rosmanol (**3**), rosmaquinone (**4**), 7-methoxyrosmanol (**5**), 7-ethoxyrosmanol (**6**), galdosol (**7**), and epirosmanol (**8**) have been obtained by partial synthesis from carnosol (**2**), an abundant natural product present in *Salvia* species. The physical and spectroscopic data of these semisynthetic diterpenes were identical to those of authentic natural samples and with data reported in the literature. These abietane diterpenes have very interesting biological activities and are present in the genus *Salvia* in low quantities; thus, the semisynthetic approach described here represents an efficient alternative method to obtain these compounds. Additionally, the known diterpene 16-hydroxyrosmanol (**10**) and a new aromatic diterpene **11** were obtained from 16-hydroxycarnosol (**9**) by reaction with Ph_3P/NBS in CH_2Cl_2. The structure of the new compound **11** was established from its spectroscopic data as 12,16-epoxycarnosol.

A member of the Lamiaceae family, the genus *Salvia* consists of some 500 species found worldwide. Since ancient times, many species of this genus have been credited with medicinal properties,[1−3] and thus merit investigation.

Some *Salvia* extracts have shown interesting biological activity such as antibacterial[4] and antioxidant,[5] and the active constituents of these species are thought to be abietatriene diterpenes. In previous works we have reported the antimicrobial and cytotoxic activities[6−8] of abietane diterpenes isolated by us from *Salvia* species, including those from the endemic Canary Islands plant *Salvia canariensis* L. (Lamiaceae). Unfortunately, most of these compounds, isolated from the aerial part of the plant, are present in very low quantities.

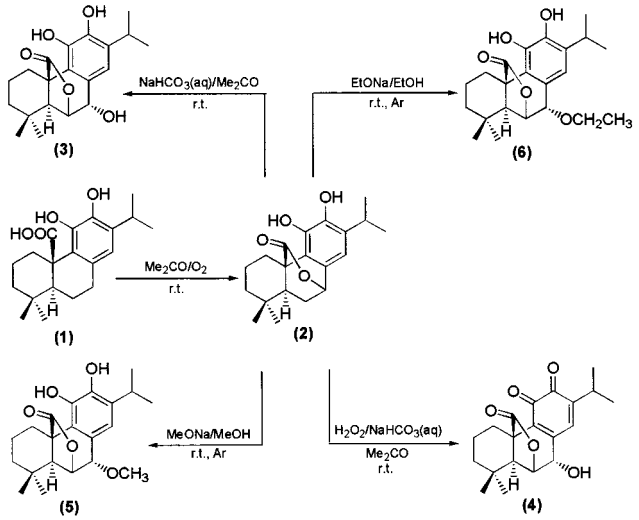
Carnosic acid[9] (**1**) and carnosol[10] (**2**) are the more abundant abietane diterpenes from some *Salvia* species. We describe here a straightforward and efficient procedure for the selective isolation of carnosic acid (**1**) and carnosol (**2**) from the aerial part of *S. canariensis* L. and an easy transformation of carnosic acid (**1**) to carnosol (**2**). To obtain the minor biologically active abietatriene diterpenes in significative quantities, we also developed efficient transformations of the abundant diterpene carnosol (**2**) to the known compounds rosmanol[11] (**3**), rosmaquinone[12] (**4**), 7-methoxyrosmanol[12] (**5**), 7-ethoxyrosmanol[12] (**6**), galdosol[13] (**7**), and epirosmanol[14] (**8**). Additionally, mild partial synthesis of 16-hydroxyrosmanol[15] (**10**) and a new diterpene **11** from 16-hydroxycarnosol[16] (**9**) are also reported.

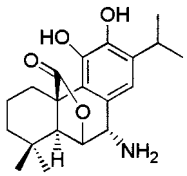
Results and Discussion

In our semisynthetic approach, we thought that the diterpenes carnosic acid (**1**) and carnosol (**2**), isolated in large quantities from the aerial part of *Salvia canariensis* L., might serve as precursors for the synthesis of other highly oxygenated abietatriene-type diterpenes that were also isolated from the genus *Salvia*.

Previously,[17] we reported some oxidation reactions of carnosic acid derivatives that might be of synthetic interest for the preparation of aromatic diterpenes with different degrees of oxidation in the A, B, and C rings. We report now the quantitative conversion of a solution of carnosic acid (**1**) in acetone, bubbled with molecular oxygen, to carnosol (**2**) (Scheme 1).

Scheme 1





(**12**)

Wenkert et al.[18] obtained the amine **12** when the leaves of *Rosmarinus officinalis* were extracted with dichloromethane and ammonia. We planned to introduce an oxygen function at C-7 by a similar procedure. Thus, treatment of an acetonic solution of carnosol (**2**) with aqueous sodium bicarbonate at room temperature gave rosmanol (**3**) as the only product (Scheme 1). On the other hand, when the above reaction was carried out with a mixture of sodium bicarbonate and hydrogen peroxide, the

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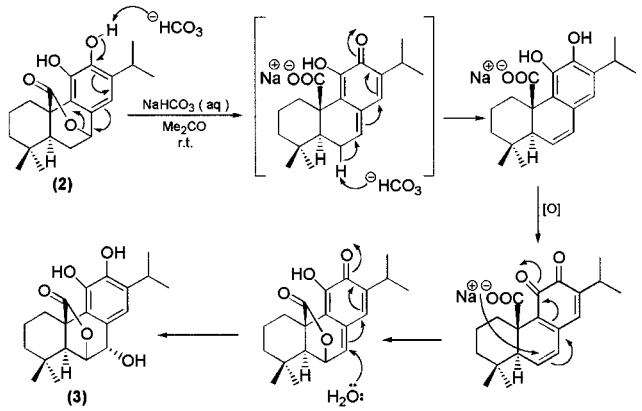
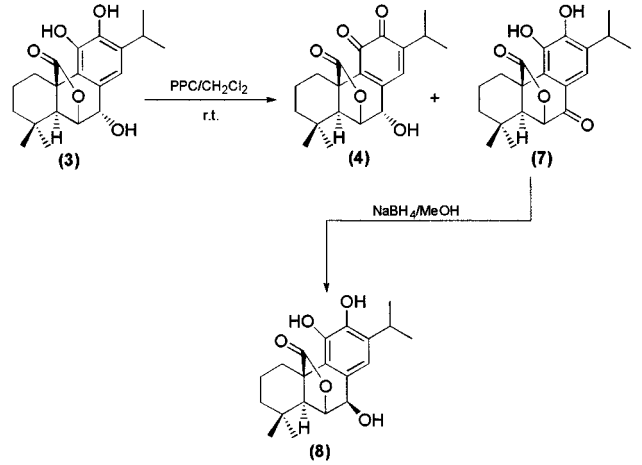
10.1021/np010565o CCC: $22.00
Published on Web 06/20/2002

Scheme 2



Scheme 3



catechol function was oxidized in situ to give rosmaquinone (**4**) (Scheme 1). All physical and spectral data of both semisynthetic rosmanol (**3**) and rosmaquinone (**4**) were identical with those reported for the natural compounds in the literature.[11,12]

Treatment of carnosol (**2**) with sodium methoxide in methanol afforded 7-methoxyrosmanol[12] (**5**) as the major product, and when carnosol (**2**) was treated with sodium ethoxide in ethanol, 7-ethoxyrosmanol[12] (**6**) was the major product (Scheme 1). The spectral and physical data of **5** and **6** were compared with those of authentic natural samples.

The transformation of carnosol (**2**) to rosmanol (**3**) shown in Scheme 1 can be rationalized through our previously reported and proven hypothesis[19,20] of a biogenetic pathway to lactonic abietatriene diterpenes in *Salvia* species, in a process such as that indicated in Scheme 2.

On the other hand, when rosmanol (**3**), obtained from carnosol (**2**), was oxidized with pyridinium chlorochromate, it gave a mixture of two products, which were separated by column chromatography and identified as rosmaquinone (**4**) and galdosol (**7**) (Scheme 3). Reduction of galdosol (**7**) with sodium borohydride in methanol afforded epirosmanol (**8**), as was to be expected from the attack of the hydride on C-7 by the less sterically hindranced *si* face of the carbonyl group. All physical and spectral data of these products were identical with those of authentic natural samples and with data reported in the literature.[12−14]

Some of the above reactions gave similar results when 16-hydroxycarnosol (**9**), also isolated from *S. canariensis* and previously reported by us from *Salvia mellifera*,[16] was used as the starting material. Thus, when a solution of 16-

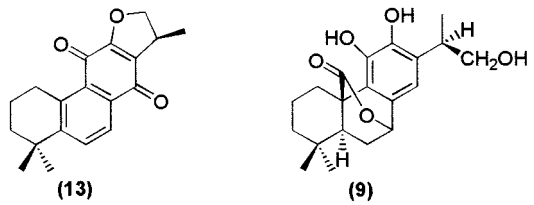
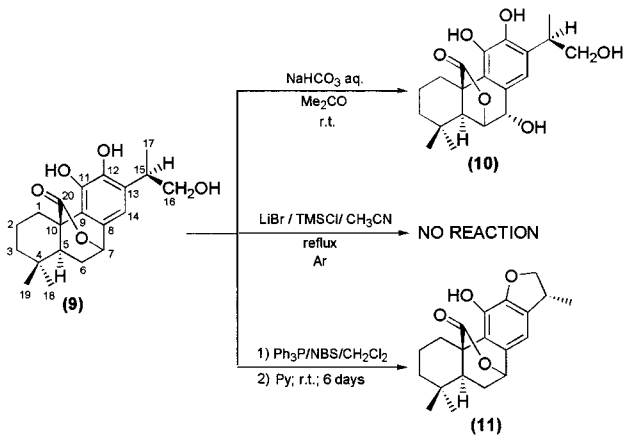


Figure 1.

Scheme 4



hydroxycarnosol (**9**) in acetone was treated at room temperature with aqueous sodium bicarbonate, 16-hydroxyrosmanol (**10**) was obtained as the only product (Scheme 4); **10** was previously isolated from *S. mellifera*.[15]

In a semisynthetic approach to isocryptotanshinone[21] (**13**) and related compounds, we chose 16-hydroxycarnosol (**9**) as the starting material. In our initial attempts, we sought to carry out the bromination reaction of 16-hydroxycarnosol (**9**) followed by base-catalyzed cyclization. When a solution of 16-hydroxycarnosol (**9**) in acetonitrile was refluxed with a mixture of LiBr/TMSCl,[22] the unaltered starting material was recovered after 12 h (Scheme 4). However, when 16-hydroxycarnosol (**9**) was magnetically stirred for 6 days at room temperature, with a solution of Ph_3P/NBS in CH_2Cl_2 and catalytic amounts of pyridine[23] (Scheme 4), the cyclization product **11** was obtained directly. The low-resolution mass spectrum of **11** showed a molecular ion $[M]^+$ at *m*/*z* 328 ($C_{20}H_{24}O_4$ by HRMS). The IR spectrum shows characteristic bands for phenol (3424 cm^{-1}) and lactone (1739 cm^{-1}) groups. In the ^1H NMR spectrum, signals for a methyl doublet (δ 1.29) and two angular methyls (δ 0.90 and 0.85) were observed. In the low-field region of the spectrum a singlet at δ 5.11 (interchangeable with D_2O) was assigned to the phenol moiety, a one-proton singlet at δ 6.59 to the aromatic H-14, and a one-proton doublet at δ 5.36 to H-7. The low chemical shift of the methyl doublet (δ 1.29) and the chemical shifts and multiplicities of the coupling constants of the signals at δ 3.56, 4.11, and 4.72 were characteristic for the H-15, H-16, and H-16′ proton signals present in the methyldihydrofuran system in isocryptotanshinone and other tanshinones.[21] This was confirmed by an HMBC experiment in which the quaternary carbon at δ 147.7 (C-12) showed long-range coupling with the AB system triplets at δ 4.11 and 4.72 (C-16, δ 79.6). The ^{13}C NMR spectrum shows signals for 20 carbon atoms, including a signal resonating at δ 175.9 (s) that is assignable to the lactonic group (C-20) and signals at δ 77.6 (d), 79.6 (t), 138.2 (s), and 147.7 (s) assignable to four carbons bearing oxygens. The NOE effect observed in a ROESY experiment between H-7 and the three-proton doublet corresponding to the methyl group on

Table 1. Data of ^{1}H NMR, ^{13}C NMR, and HMBC of Compound **11** in $CDCl_3$

position	δ_H[a]	δ_C[b]	HMBC[c]
1	α 2.46 td (J_1 = 4.4, J_2 = 14.0)	28.9 (t)	2*, 3, 5, 9, 10*, 20
	β 2.88 br d (J = 14.3)		
2	1.65 dt	18.8 (t)	
	1.97 m		
3	1.51 br d (J = 13.0)	41.0 (t)	
	1.24 m		
4		34.4 (s)	
5	1.71 m	45.3 (d)	4*, 6*, 9, 10*, 18, 19, 20
6	1.87 m	29.7 (t)	4, 5*, 7*, 8, 10
	2.18 m		
7	5.36 d (J = 3.8)	77.6 (d)	5, 9, 14, 20
8		133.5 (s)	
9		123.7 (s)	
10		48.8 (s)	
11	5.11 s (O*H*)	138.2 (s)	9, 11*, 12
12		147.7 (s)	
13		130.6 (s)	
14	6.59 s	110.1 (d)	7, 9, 12, 15
15	3.56 sext (J = 7.6)	37.3 (d)	12, 13*, 16*, 17*
16	4.11 t (J = 7.0)	79.6 (t)	12, 13, 15*, 17
	4.72 t (J = 8.8)		
17	1.29 d (J = 7.0)	19.0 (q)	13, 15*, 16
18	0.90 s	19.7 (q)	3, 4*, 5, 19
19	0.85 s	31.7 (q)	3, 4*, 5, 18
20		175.9 (s)	

[a] δ in ppm, J values in Hz. [b] δ in ppm; data are based on DEPT and HSQC experiments. [c] *: two-bond coupling enhancement observed.

C-15 confirmed the relative configuration of C-15 with the methyl group in the α-position. This is in accordance with the absolute configuration of C-15 in the starting material **9**[16] and the S_N2 conditions of the cyclization reaction.

All the above data, together with the ^{13}C NMR, COSY, HSQC, and HMBC experiments (see Table 1), are in accordance with the structure of 12,16-epoxycarnosol for **11**.

Experimental Section

General Experimental Procedures. The NMR spectra were recorded on Bruker Avance 300 MHz and Bruker Avance 400 MHz spectrometers in $CDCl_3$, unless otherwise noted. Chemical shifts are given in ppm with TMS as the internal standard. IR spectra were obtained on a Bruker IFS 28/55 (FTIR) spectrometer and UV spectra on a JASCO V-560. Low-resolution mass spectra were run on a VG Micromass ZAB-2F and high-resolution mass spectra on a VG Micromass ZAB-2F at 70 eV. Merck silica gel (0.063−0.200) was used for column chromatography. Analytical thin-layer chromatography (TLC) and preparative TLC were carried out on precoated Schleicher and Schüll plates. A voucher specimen of *Salvia canariensis* L. (no. 25252) was deposited with the herbarium of the Department of Botany, Faculty of Biology, Univesidad de La Laguna.

Isolation of Carnosic Acid (1) and Carnosol (2). Dried stems and leaves of *Salvia canariensis* L. (1.5 kg) were extracted with distilled acetone (10 L × 3) at room temperature, and the solvent was removed under reduced pressure at 40 °C, yielding 112.65 g of a dried extract. The extract was dissolved in ethyl acetate (250 mL), transferred to a separatory funnel, and treated with 1 N sodium hydroxide (250 mL × 5). Each basic fraction was acidified with 5% hydrochloric acid until the mixture was acidic by pH indicator and then extracted with ethyl acetate (300 mL × 3). The organic layers were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Fractions 2−5 were mixed and subjected to chromatography on Sephadex LH-20 using a mixture of *n*-hexane/dichloromethane/methanol (2:1:1) as eluent. After TLC analysis of the 24 fractions colleted, fractions 11−15 were purified by crystallization with a mixture of dichloromethane and acetone, yielding carnosol[10] (**2**) (1.8 g). Fractions 20−24 were purified by silica gel column chromatography using mixtures of dichloromethane/acetone of increasing polarity to yield the following known products: carnosic acid[9] (**1**) (805.6 mg), rosmanol[11] (**3**) (161.7 mg), carnosol[10] (**2**) (277.7 mg), and 16-hydroxycarnosol[16] (**9**) (160 mg).

Oxidation of Carnosic Acid (1). A solution of **1** (132.2 mg, 0.398 mmol) in acetone (30 mL) was bubbled with molecular oxygen (0.1 bar) at room temperature for 4 h. After this time, the acetone was evaporated in vacuo to give carnosol[10] (**2**) (130 mg, quantitative yield) as a white solid: mp 212−213 °C; UV (EtOH) λ_{max} (log ϵ) 210 (4.42), 284 (3.40) nm; IR (film) ν_{max} 3495, 3390, 2980, 2870, 1710, 1580, 1480, 1450, 1350, 1200 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.86 (3H, s, Me-19), 0.90 (3H, s, Me-18), 1.22 (6H, d, J = 7.0 Hz, Me-16 and Me-17), 1.31 (1H, dd, J_1 = 3.5 Hz, J_2 = 14.0 Hz, H-3α), 1.73 (1H, q, H-5), 1.90 (1H, td, H-6β), 1.99 (1H, dt, H-2β), 2.20 (1H, m, H-6α), 2.33, 2.39, 2.46 (1H, td, J_1 = 4.3 Hz, J_2 = 14.0 Hz, H-1α), 2.90 (1H, br d, H-1β), 3.08 (1H, hept, J = 7.0 Hz, H-15), 5.26 (1H, br s, Ar-O*H*), 5.37 (1H, dd, J_1 = 1.4 Hz, J_2 = 4.0 Hz, H-7), 5.73 (1H, br s, Ar-O*H*), 6.64 (1H, s, H-14); EIMS m/z 330 [M]$^+$ (22), 286 (100), 271 (9), 243 (7), 215 (30).

Treatment of Carnosol (2) with Aqueous Sodium Bicarbonate. Carnosol (**2**) (52.1 mg, 0.158 mmol) in acetone (5 mL) was treated with aqueous sodium bicarbonate (5%, 6 mL, 3.57 mmol), and the mixture was stirred at room temperature for 6.5 h, after which the acetone was evaporated under reduced pressure. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl acetate, washed with brine, and dried over anhydrous sodium sulfate. The residue was purified by silica gel column chromatography eluting with *n*-hexane/acetone (4:1), yielding rosmanol[11] (**3**) (39.5 mg, 72%): ^{1}H NMR (300 MHz) δ 0.93 (3H, s, Me-19), 1.03 (3H, s, Me-18), 1.22, 1.23 (each 3H, d, J = 7.0 Hz, Me-16 and Me-17), 2.00 (1H, td, H-1α), 2.21(1H, s, H-5), 3.20 (1H, hept, J = 7.0 Hz, H-15), 3.21 (1H, br d, H-1β), 4.57 (1H, d, J = 3.3 Hz, H-6), 4.74 (1H, d, J = 3.3 Hz, H-7), 6.87 (1H, s, H-14); EIMS m/z 346 [M]$^+$ (100), 300 (48), 287 (62), 284 (41), 273 (38), 269 (31), 231 (51), 215 (51); HREIMS m/z 346.1798 (calcd for $C_{20}H_{26}O_5$ 346.1779).

Treatment of Carnosol (2) with Hydrogen Peroxide/Sodium Bicarbonate. To a solution of carnosol (**2**) (10.3 mg, 0.031 mmol) in acetone (2.5 mL) was added solid sodium bicarbonate (32.2 mg, 0.38 mmol) and hydrogen peroxide (35%, 0.14 mL, 1.56 mmol). The mixture was stirred at room temperature for 45 min, the solvent was removed under reduced pressure, the mixture was cooled in an ice-bath, water was added, and the product was extracted with ethyl acetate, washed with brine, and dried with anhydrous sodium sulfate. The crude reaction product was purified by preparative TLC using *n*-hexane/acetone (7:3) as eluent to give rosmaquinone[12] (**4**) (7.5 mg, 70%): ^{1}H NMR (300 MHz) δ 0.88 (3H, s, Me-19), 1.02 (3H, s, Me-18), 1.11, 1.12 (each 3H, d, J = 7.0 Hz, Me-16 and Me-17), 2.05 (1H, s, H-5), 2.93 (1H, hept, J = 7.0 Hz, H-15), 3.21 (1H, br d, J = 10.5 Hz, H-1β), 4.40 (1H, d, J = 3.3 Hz, H-6), 4.52 (1H, d, J = 3.3 Hz, H-7), 6.79 (1H, s, H-14); EIMS m/z 344 [M]$^+$ (15), 257 (48), 230 (44), 229 (38), 215 (33), 203 (45), 201 (48), 187 (43), 128 (39), 115 (57), 91 (66), 55 (100); HREIMS m/z 344.1586 (calcd for $C_{20}H_{24}O_4$ 344.1548).

Treatment of Carnosol (2) with Sodium Methoxide. A mixture of carnosol (**2**) (68.6 mg, 0.208 mmol) and sodium methoxide (145.3 mg, 2.69 mmol) in methanol (5 mL) was stirred at room temperature for 12 h. The mixture was cooled in an ice-bath and a solution of 5% hydrochloric acid added until the reaction mixture was acidic. The methanol was evaporated under reduced pressure, the product was extracted with ethyl acetate, and the organic layers were washed with brine and dried over anhydrous sodium sulfate. The crude product was purified by silica gel column chromatography eluting with dichloromethane/acetone (98:2) to obtain 7-methoxyrosmanol[12] (**5**) (29.5 mg, 39%): ^{1}H NMR (300 MHz) δ 0.94 (3H, s, Me-19), 1.02 (3H, s, Me-18), 1.23 (6H, d, J = 7.0 Hz,

Me-16 and Me-17), 2.00 (1H, td, H-1α), 2.25 (1H, s, H-5), 3.07 (1H, hept, J = 7.0 Hz, H-15), 3.17 (1H, br d, H-1β), 3.66 (3H, s, $-OCH_3$), 4.27 (1H, d, J = 3.18 Hz, H-6), 4.71 (1H, d, J = 3.18 Hz, H-7), 5.48 (1H, br s, Ar-O*H*), 6.00 (1H, br s, Ar-O*H*), 6.80 (1H, s, H-14); EIMS *m/z* 360 $[M]^+$ (100), 314 (81), 298 (80), 284 (88), 269 (84), 245(93), 228 (38), 215 (93); HREIMS *m/z* 360.1931 (calcd for $C_{21}H_{28}O_5$ 360.1926).

Treatment of Carnosol (2) with Sodium Ethoxide. A solution of sodium (48.9 mg, 2.13 mmol) in ethanol (10 mL) was stirred at room temperature under nitrogen. When the sodium was dissolved, a solution of carnosol (**2**) (49 mg, 0.148 mmol) in ethanol (5 mL) was added. After 12 h, the reaction mixture was acidified with dilute hydrochloric acid, the ethanol was evaporated under reduced pressure, and the product was extracted with ethyl acetate, washed with brine, and dried over anhydrous sodium sulfate. The crude reaction product was chromatographed over silica gel using dichloromethane/acetone (98:2) as eluent to yield 7-ethoxyrosmanol[12] (**6**) (28.2 mg, 51%): ^{1}H NMR (300 MHz) δ 0.92 (3H, s, Me-19), 1.01 (3H, s, Me-18), 1.22 (6H, d, J = 7.0 Hz, Me-16 and Me-17), 1.33 (3H, t, $-OCH_2$-CH_3), 1.99 (2H, td, H-1α), 2.28 (1H, s, H-5), 3.11 (1H, hept, J = 7.0 Hz, H-15), 3.20 (1H, br d, H-1β), 3.84 (2H, q, $-OCH_2$-CH_3), 4.36 (1H, d, J = 3.20 Hz, H-6), 4.66 (1H, d, J = 3.20 Hz, H-7), 5.59 (1H, br s, Ar-O*H*), 6.15 (1H, br s, Ar-O*H*), 6.79 (1H, s, H-14); EIMS *m/z* 374 $[M]^+$ (100), 328 (87), 300 (29), 231 (24), 215 (68), 69 (40), 55 (51); HREIMS *m/z* 374.2084 (calcd for $C_{22}H_{30}O_3$ 374.2075).

Oxidation of Rosmanol (3) with Pyridinium Chlorochromate. Rosmanol (**3**) (39.5 mg, 0.11 mmol) in dichloromethane (15 mL) was treated at room temperature and under magnetic stirring with pyridinium chlorochromate (47.8 mg, 0.22 mmol). After 2.5 h the reaction was completed. The mixture was filtered through a short pad of Florisil with suction, the filtrate was evaporated on the rotary evaporator, and the crude product was chromatographed on silica gel using *n*-hexane/dioxane (1:1) as eluent to give in increasing order of polarity galdosol[13] (**7**) (3.9 mg, 21%) and rosmaquinone[12] (**4**) (6.1 mg, 32%). Galdosol (**7**): ^{1}H NMR (300 MHz) δ 0.98 (3H, s, Me-19), 1.12 (3H, s, Me-18), 1.18 and 1.29 (each 3H, d, J = 7.0 Hz, Me-16 and Me-17), 2.46 (1H, s, H-5), 3.20 (1H, hept, J = 7.0 Hz, H-15), 4.72 (1H, s, H-6), 7.69 (1H, s, H-14). Rosmaquinone (**4**): the spectroscopic data are given above.

Reduction of Galdosol (7) with Sodium Borohydride. Galdosol (**7**) (3.9 mg, 0.011 mmol) was dissolved in methanol (2 mL) and treated with sodium borohydride (19.3 mg, 0.51 mmol). The mixture was stirred at room temperature for 4.5 h, then the mixture was cooled in an ice-bath, acidified with a solution of 5% hydrochloric acid, extracted with ethyl acetate, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the crude product was purified by preparative TLC using *n*-hexane/ethyl acetate (3:2) as eluent to yield epirosmanol[14] (**8**) (3.4 mg, 90%): ^{1}H NMR (300 MHz) δ 0.95 (3H, s, Me-19), 1.00 (3H, s, Me-18), 1.23 (6H, d, J = 7.0 Hz, Me-16 and Me-17), 1.97 (1H, s, H-5), 3.08 (1H, hept, J = 7.0 Hz, H-15), 3.19 (1H, br d, H-1β), 4.77 (2H, overlapping signals, H-6 and H-7), 5.50 (1H, br s, Ar-O*H*), 6.18 (1H, br s, Ar-O*H*), 7.04 (1H, s, H-14); EIMS *m/z* 346 $[M]^+$ (24), 300 (9), 284 (34), 231 (38), 215 (100), 199 (43), 14 (44); HREIMS *m/z* 346.1779 (calcd for $C_{20}H_{26}O_5$ 346.1778).

Treatment of 16-Hydroxycarnosol (9) with Aqueous Sodium Bicarbonate. 16-Hydroxycarnosol (**9**) (39.2 mg, 0.11 mmol) in acetone (5 mL) was treated with aqueous sodium bicarbonate (5%, 10 mL, 6 mmol) for 15.5 h. The solvent was evaporated under reduced pressure, the mixture was cooled in an ice-bath, water was added, and the product was extracted with ethyl acetate, washed with brine, and dried over anhydrous sodium sulfate. The crude reaction was chromatographed over silica gel with dichloromethane/acetone (98:2) to obtain 16-hydroxyrosmanol[15] (**10**) (17.0 mg, 43%): ^{1}H NMR (300 MHz) δ 0.92 (3H, s, Me-19), 1.02 (3H, s, Me-18), 1.32 (3H, d, J = 7.0 Hz, Me-17), 2.21 (1H, s, H-5), 3.09 (1H, sext, J = 7.0 Hz, H-15), 3.29 (1H, br d, J = 14.6 Hz, H-1β), 3.76 (1H, dd, J_1 = 2.7 Hz, J_2 = 9.5 Hz, H-16), 3.99 (1H, dd, J_1 = 2.7 Hz, J_2 = 9.5 Hz, H-16), 4.51 (1H, d, J = 3.4 Hz, H-6), 4.72 (1H, d, J = 3.4 Hz, H-7), 6.37 (1H, s, Ar-O*H*), 6.69 (1H, s, H-14), 8.98 (1H, s, Ar-O*H*); EIMS *m/z* 362 $[M]^+$ (25), 344 (4), 300 (25), 267 (39), 213 (43), 97 (42), 83 (55), 57 (93), 55 (100); HREIMS *m/z* 362.1694 (calcd for $C_{20}H_{26}O_6$ 362.1659).

12,16-Epoxycarnosol (11). A solution of triphenylphosphine (221.8 mg, 0.846 mmol) in dichloromethane (10 mL) was added dropwise to a solution of *N*-bromosuccinimide (145.7 mg, 0.819 mmol) in dichloromethane (7.5 mL), and the mixture was stirred at room temperature for 5 min. Pyridine (0.03 mL, 0.372 mmol) was then added dropwise to the solution followed by addition of 16-hydroxycarnosol (**9**) (93.8 mg, 0.271 mmol). The reaction mixture was stirred at room temperature for 6 days, then poured into a saturated aqueous sodium bicarbonate solution. The product was extracted with ethyl acetate, washed with water and brine, and dried over anhydrous sodium sulfate. The crude product was chromatographed over silica gel using dichloromethane/acetone (99:1) as eluent to give **11** (59.7 mg, 67%) as a white solid: mp 138−140 °C; UV (EtOH) λ_{max} (log ϵ) 209 (1.80), 268 (2.92) nm; IR (film) ν_{max} 3424, 2957, 1739, 1476, 1393, 1339, 1115, 756 cm^{-1}; ^{1}H NMR (300 MHz, see Table 1); ^{13}C NMR (75 MHz, see Table 1); EIMS *m/z* 328 $[M]^+$ (14), 284 (50), 282 (100), 280 (35), 267 (69), 213 (40), 165 (11), 111 (21), 55 (50); HREIMS *m/z* 328.1647 (calcd for $C_{20}H_{24}O_4$ 328.1675).

Acknowledgment. We thank FEDER (Grant No. IFD97-0602) and the CYTED Project IV.11 for financial support.

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NP010565O