Synthesis of Analogues of *Eunicea* γ-Cembranolides Containing Cyclic Ethers via Saponification†

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A method for the synthesis of derivatives of the lead structures euniolide (**1**), 12,13-bisepieupalmerin (**2**), and eupalmerin acetate (**3**) containing tetrahydrofuran and tetrahydropyran ring systems was developed on the basis of alkali-induced intramolecular oxacyclizations. Representatives of the new analogues were submitted to the in vitro antitumor cell-line-screening program of the National Cancer Institute (NCI). While it was shown that a variety of structural modifications are possible, these transformations led typically to nontoxic synthetic cembranoids.

Caribbean gorgonian octocorals of the *Eunicea* genus represent an abundant source of structurally interesting cembranolide diterpenes.[1−3] Naturally occurring cembranoids such as euniolide (**1**),[4] 12,13-bisepieupalmerin (**2**),[5] and eupalmerin acetate (**3**)[6] have been shown to possess potent in vitro antitumor activity (Figure 1).[3] In addition, a series of analogues of *Eunicea* cembranolides containing cyclic ethers was reported to possess potent antileukemic activities.[7] To develop agents with useful biological properties, we have synthesized a series of unusual analogues of cembranolides **1**−**3** containing cyclic ether ring systems. Concomitant hydrolysis and intramolecular oxacyclization of these abundant α-methylene-γ-lactones mediated by alkali were the key steps for the present syntheses. These studies have helped to establish a database of sufficient size to be useful in future efforts directed at the ^{1}H and ^{13}C NMR based structure elucidations of new cembranoids.

Results and Discussion

The Caribbean gorgonian species *E. succinea* and *E. mammosa* contain substantial amounts of extractable organic matter and grow in shallow waters; they are hence easily collected. The hexane extracts obtained from each species were chromatographed to give euniolide (**1**), 12,13-bisepieupalmerin (**2**), and eupalmerin acetate (**3**) as white crystalline solids in multigram amounts. The complete structural assignments of all the synthetic cembranoid analogues described in the present work were accomplished on the basis of comprehensive 2D NMR experiments involving ^{1}H−^{1}H COSY, DEPT, ^{1}H−^{13}C COSY (CSCMBB), HMQC, and HMBC measurements. In most cases, these 2D NMR spectra provided both the structure and the complete proton and carbon atom assignments. Since starting materials **1**−**3** were optically pure without ambiguity in the absolute configuration, the absolute configurations of the synthetic analogues are as depicted.

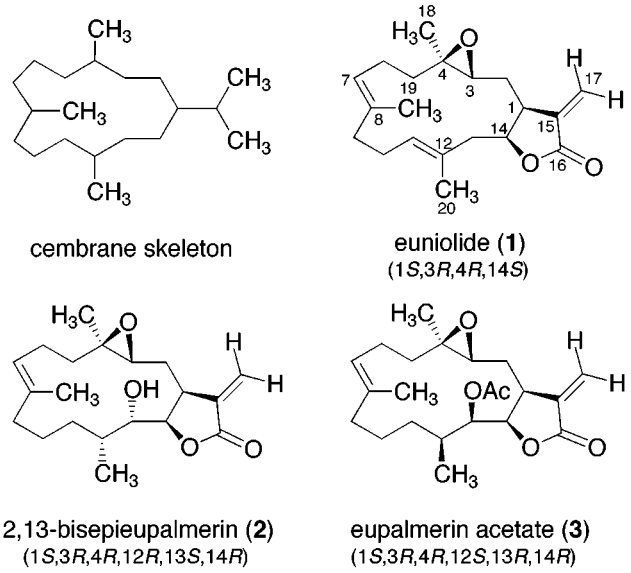

Figure 1. Cembrane carbon skeleton and absolute structures of euniolide (**1**), 12,13-bisepieupalmerin (**2**), and eupalmerin acetate (**3**).

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§ Graduate student sponsored by the NIH-MBRS and NSF-MRCE Programs of the University of Puerto Rico.

|| Undergraduate student sponsored by the NIH-MBRS Program of the University of Puerto Rico.

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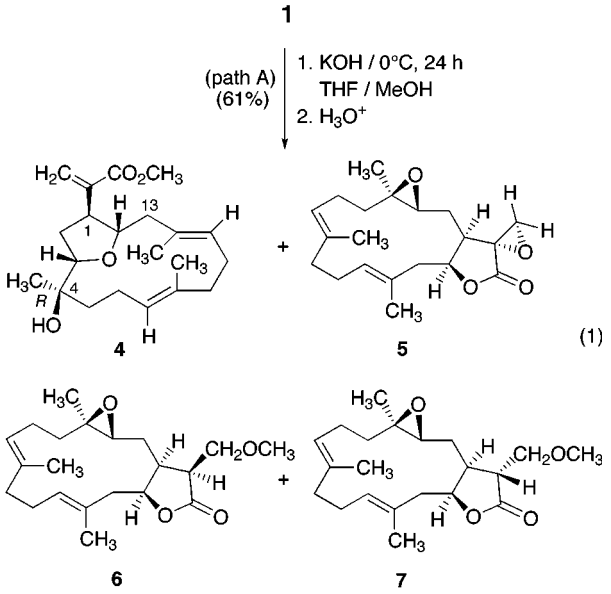
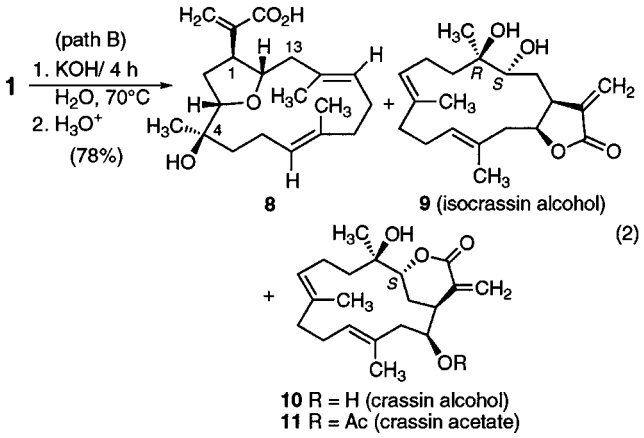
(A) Saponification of Euniolide (1). Our first attempt at structural modification of euniolide (**1**) involved tandem base-induced hydrolysis of the γ-lactone and rearrangement of the epoxide to form an oxa-bridge between C-3 and C-14 (eq 1). Thus, euniolide was treated



(1)

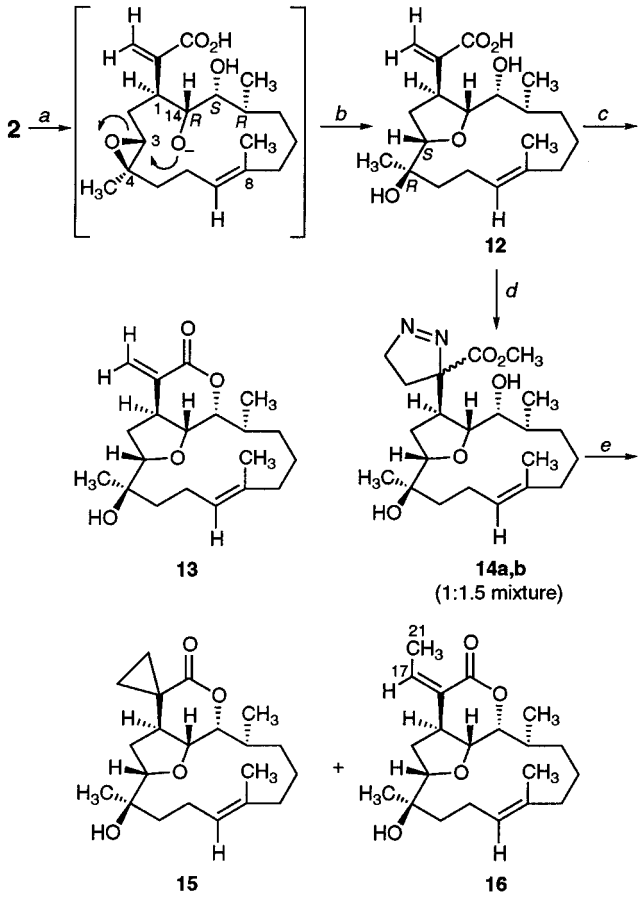
with KOH/THF−MeOH at 0 °C for 24 h, followed by 0.1 N HCl, giving the desired furan ether **4** and products **5**−**7** in 61% overall yield, with 38% of the starting material **1** also recovered. It is especially noteworthy that in no instance was direct conversion of the C-3,4 epoxide to a diol functionality observed. A mechanistic rationale for the unexpected formation of α,β-epoxy-γ-lactone **5** (isolated in 13% yield) invoking the intervention of THF−hydroperoxide has been outlined as Supporting Information. Conjugate additions furnished a 2:1 mixture of epimeric lactones **6** and **7** in moderate yield (35%). Nucleophilic attack on the lactone carbonyl left an alkoxyl anion at C-14, which after a regiospecific attack at C-3 of the epoxide, furnished eunioloic acid methyl ester (**4**) in 13% yield.

In sharp contrast, hot aqueous KOH reacted very cleanly with euniolide (**1**), affording a 1.4:1.3:1 mixture of eunioloic acid (**8**), isocrassin alcohol (**9**),[4b] and crassin alcohol (**10**)[8] in very good overall yield (78%) after neutralization with 0.1 N HCl (eq 2).[9] To ensure reproducible high yields in our reaction, sonication of a suspension of euniolide in 3% aqueous KOH turned out



(2)

Scheme 1[a]



[a] Reaction conditions: (a) KOH, H_2O, 90−100 °C, 22 h; (b) 5 N HCl, 25 °C, 63%; (c) benzene, AcOH, 65−70 °C, 120 h, 98%; (d) CH_2N_2, ether−CH_2Cl_2, 25 °C, 30 min, 100%; (e) toluene, AcOH, 110−120 °C, 4.5 h, 51%.

to be essential. To confirm the structure of translactonization product **10** we treated it with acetic anhydride in the presence of pyridine in CH_2Cl_2 at 25 °C for 24 h to afford the known δ-cembranolide crassin acetate (**11**) in 71% isolated yield (eq 2).[10]

(B) Saponification of 12,13-Bisepieupalmerin (2). Next was a synthetic pathway leading to analogues of 12,13-bisepieupalmerin (**2**) possessing a cyclic ether array. The saponification of **2** with aqueous KOH, outlined in Scheme 1, surprisingly afforded only one of several possible products, but it was not the translactonized cembra-16,3-olide analogue. Instead, furan ether 12,13-bisepieupalmeroic acid (**12**) was isolated in 63% yield. Through acid-promoted cyclization of carboxylic acid **12**, which has the favorable 1*S*,13*S* configuration, we efficiently achieved the synthesis of 12,13-bisepieupalmerolide (**13**) in 98% yield. Compound **12** gave pyrazoline adducts **14a**,**b** with diazomethane at 25 °C for 30

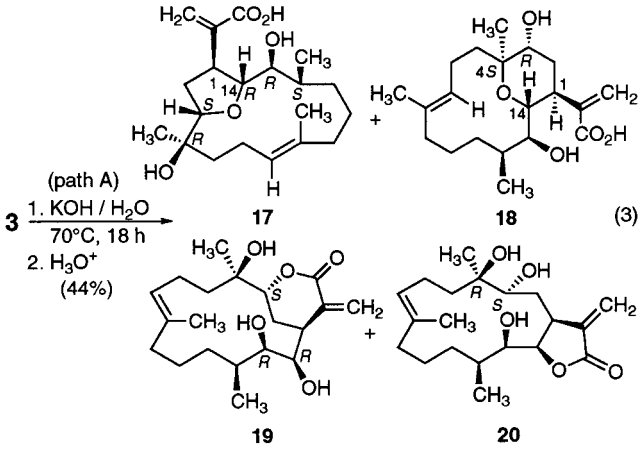
(8) (a) Marshall, J. A.; Royce, R. D., Jr. *J. Org. Chem.* **1982**, *47*, 693−698. (b) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942−6949. (c) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8928−8929.

(9) During a series of lactone interconversion studies, Marshall and co-workers saponified crassin alcohol (**10**) and isolated isocrassin alcohol (**9**) by a sequence involving several steps. They also found that treatment of isocrassin alcohol with aqueous potassium hydroxide followed by acidification leads cleanly to crassin alcohol (**10**); see ref 4b.

(10) (a) Martin, G. E.; Matson, J. A.; Turley, J. C.; Weinheimer, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 1888−1890. (b) Look, S. A.; Fenical, W.; Qi-tai, Z.; Clardy, J. *J. Org. Chem.* **1984**, *49*, 1417−1423.

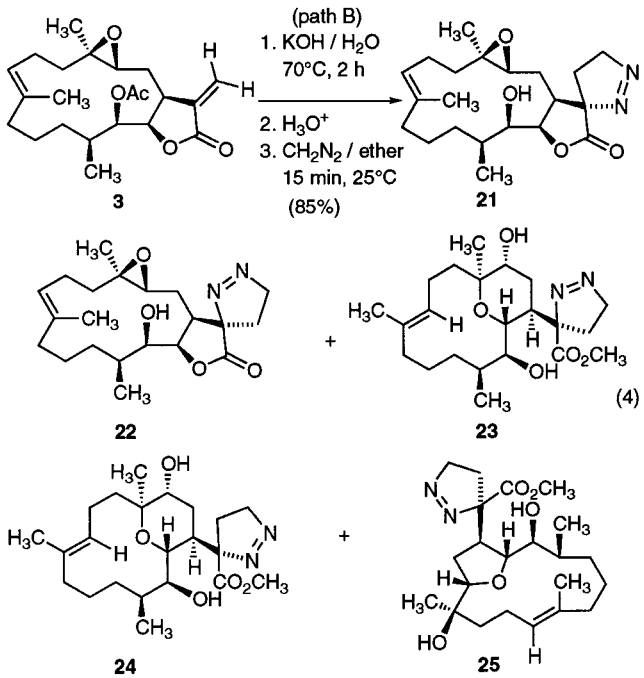
min in quantitative yield as a 1:1.5 mixture.[11] In turn, the derived esters were smoothly cyclized to δ-lactones **15** and **16** in good overall yield (51%) through AcOH-promoted lactonization and thermolysis in refluxing toluene.

(C) Saponification of Eupalmerin Acetate (3). Interestingly, our initial run of **3** through a similar saponification sequence produced a 14:11:3:1 mixture of 3,14-eupalmeroic acid (**17**), 4,14-eupalmeroic acid (**18**), eucrassin alcohol (**19**), and isoeucrassin alcohol (**20**) in 44% yield (eq 3). These results stand in sharp contrast

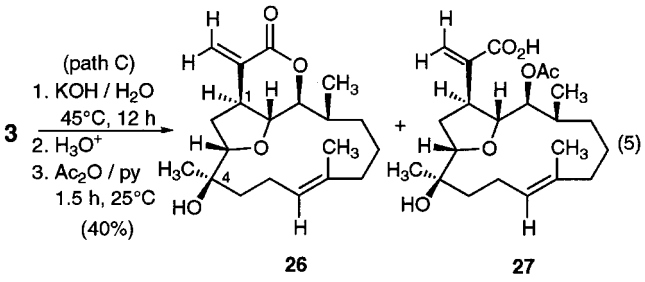


to our previous findings with the saponification of 12,13-bisepieupalmerin (**2**, Scheme 1). Our principal concern was whether carboxylic acids such as **17** and **18**, possessing the seemingly unfavorable 1*S*,13*R* stereochemistry, would undergo further intramolecular cyclization to their corresponding lactones (vide infra). We suspected that translactonization of kinetic isoeucrassin alcohol (**20**) afforded the thermodynamically more stable δ-lactone eucrassin alcohol (**19**).

A second trial, where the same saponification sequence was run for only 2 h followed by workup and treatment with diazomethane, gave a mixture in 85% yield of pyrazolines **21**−**25** (eq 4). Interestingly, under these



reaction conditions the formation of **19** and **20** was completely suppressed. Instead, an easily separable mixture of pyrazolines **21** and **22** (obtained in a 1.7:1 ratio, respectively) and **23** and **24** (obtained in a 1.5:1 ratio, respectively) was obtained. Surprisingly, **25** was isolated as a single diastereomer in 24% yield. A third saponification trial afforded a 1:1 mixture of eupalmerolide (**26**) and carboxylic acid **27** in moderate isolated yield (40%) upon treatment of the crude with a mixture of acetic anhydride and pyridine at 25 °C for 1.5 h (eq 5). Starting material **3** was also recovered. In the latter



attempt, which ran for only 12 h at a lower temperature (45 °C), carboxylic acid 3,14-eupalmeroic acid (**17**), the kinetic product, predominated.

In our last saponification, we ran the reaction at 45 °C again, but allowed a longer reaction time (18 h). In this run, however, after neutralization with 5 N HCl, we subjected the products without further purification to the ozonolytic protocol outlined in Scheme 2. This afforded the C_{18} carboxylic acids **28** and **29** in 30 and 54% isolated yield, respectively. Because it was expected that esterification of these highly functionalized carboxylic acids would lead to more manageable products (the chromatographic separation of **28** and **29** was problematic and **29** was sparingly soluble in most organic solvents), each product was treated separately with diazomethane at 25 °C, thereby avoiding subsequent yield-lowering chromatography. An attempt to purify the former crude by chromatography through a short plug of silica gel (Sep-Pak) led in nearly quantitative yield to **30**, a structurally interesting furan ether containing a γ-lactone and a cyclic hemiacetal. Crude **31** (obtained in 96% yield) was analyzed without further purification. No attempt was made at this time, however, to further cyclize diester **31** through successive acid-mediated intramolecular transesterifications.

Photolysis of pyrazoline **23** at 25 °C for 2.5 h afforded derivative **32** as the only isolated product in quantitative yield (Scheme 3). Sadly, treatment of **32** with PTSA·H_2O in refluxing chloroform resulted in a high (80%) recovery of the starting material and none of the desired lactone **33**. Considerable experimentation with a wide range of acid catalysts led to partial or complete decomposition of **32** or no reaction. Pyrazoline **25** was likewise subjected to the photolytic protocol depicted in Scheme 4. Like its pyran ether counterpart **23**, pyrazoline **25** underwent rapid and quantitative conversion to **34**. If, on the other hand, a 7-59 Corning filter was used at 25 °C for 13 h, **34** was once again produced, but only in 88% yield, and smaller amounts of photoproducts **35** and **36** were also obtained. When **25** was decomposed thermally in benzene and glacial acetic acid at 90−100 °C, a 3:1 mixture of

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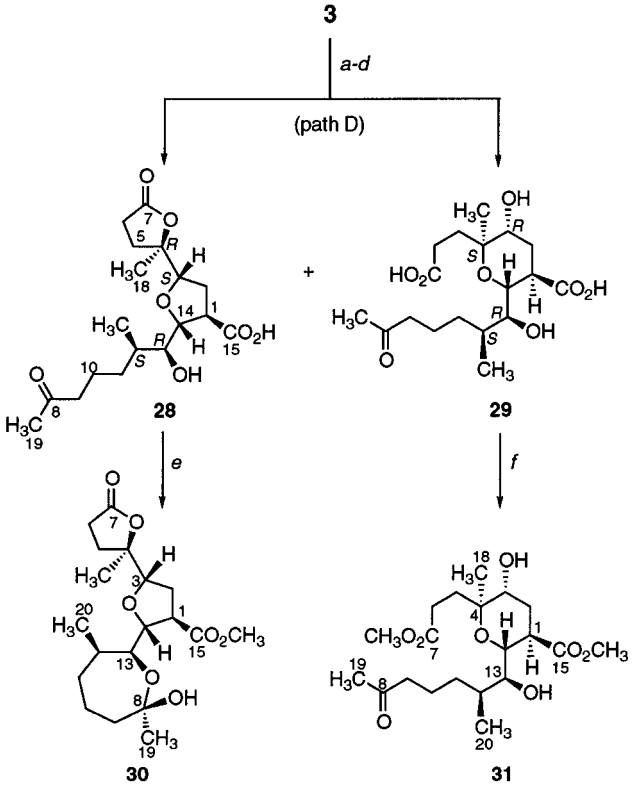
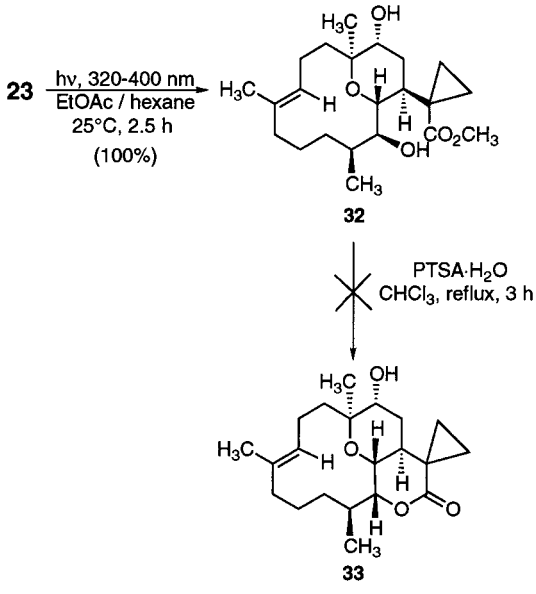
Scheme 2[a]



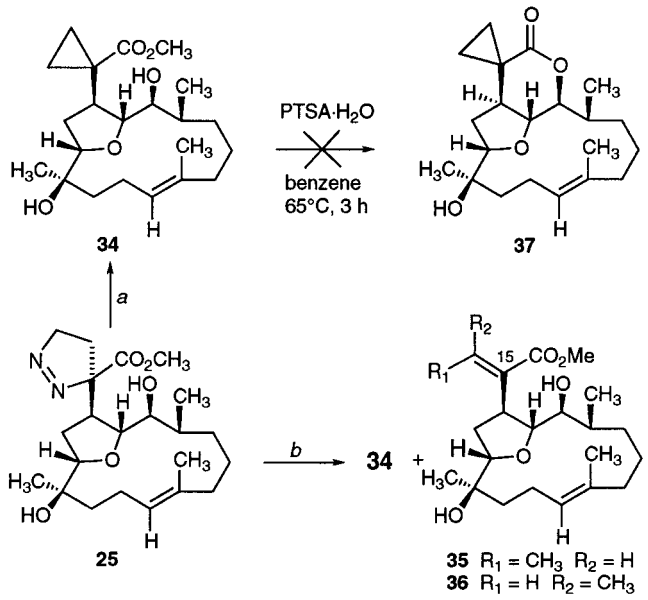
[a] Reaction conditions: (a) KOH, H_2O, 45 °C, 18 h; (b) 5 N HCl, 25 °C; (c) EtOAc, O_3, −78 °C; (d) H_2O_2, H_2O, Δ, 18 h, 84%; (e) CH_2N_2, 25 °C, 30 min, Sep-Pak, 90%; (f) CH_2N_2 in ether, MeOH−$CHCl_3$, 25 °C, 30 min, 96%.

Scheme 3



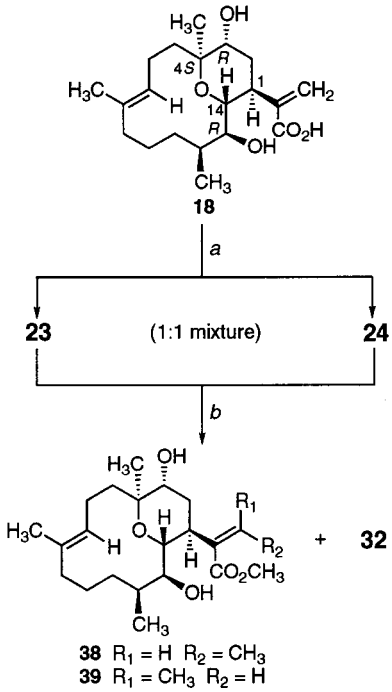
products **34** and **36** was obtained in 75% overall yield. It was subsequently found that exposure of ester **34** to either glacial acetic acid or PTSA·H_2O in refluxing benzene did not produce the desired cyclization product **37** (Scheme 4). Furthermore, treatment of **25** with PTSA·H_2O in benzene using temperatures varying from 25 to 65 °C also failed to furnish the corresponding δ-lactone. Thus, ester derivatives **25**, **32**, and **34**, each having the 1*S*,13*R* configuration, did not undergo further cyclization through intramolecular transesterifications. These results stand in sharp contrast to our previous finding with the mixture of pyrazolines **14a**,**b** (Scheme 1).

Scheme 4[a]



[a] Reaction conditions: (a) EtOAc−hexane, *hν* (320−400 nm), 25 °C, 30 min, 100%; (b) EtOAc−hexane, *hν* (320−400 nm), 7-59 Corning filter, 25 °C, 13 h, 100%.

Scheme 5[a]

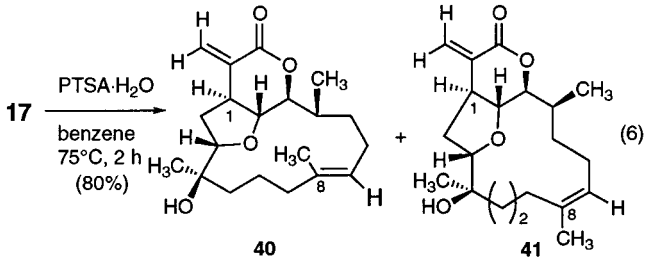


[a] Reaction conditions: (a) CH_2N_2 in ether−CH_2Cl_2, 25 °C, 30 min, 76%; (b) toluene, AcOH, 115 °C, 4.5 h, 42%.

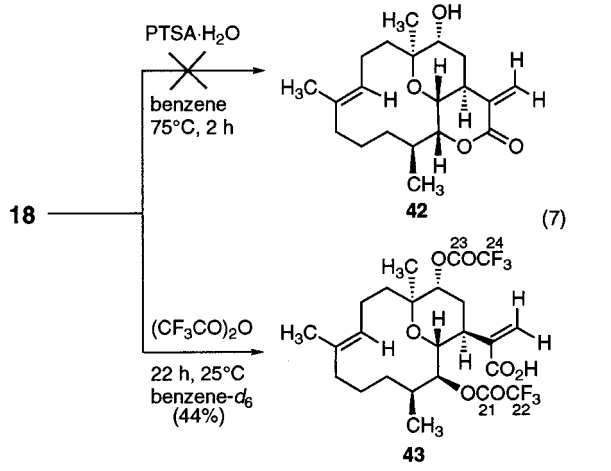
The reaction of 4,14-eupalmeroic acid (**18**) with diazomethane was carefully reexamined using not crude but pure starting material. Using the same temperature and reaction time as in carboxylic acid **12**, isomer **18** furnished a 1:1 mixture of **23** and **24** in 76% overall yield (Scheme 5). The latter mixture of pyrazolines was refluxed for 4.5 h in toluene and acetic acid to give, in 42% overall yield, a 15:12.5:1 mixture of **32**, **38**, and **39**. This was a one-pot reaction in which a solution of **18** and

diazomethane in ether−CH_2Cl_2 was stirred at ambient temperature for 30 min. After the reaction mixture was concentrated, the pyrazolines were dissolved in a mixture of toluene and acetic acid, and the solution was heated to 115 °C for 4.5 h, cooled, and concentrated under vacuum. The oily residue obtained was purified by column chromatography. Under these reaction conditions, no tricyclic products arising from further acid-catalyzed intramolecular transesterification were formed.

With the failure of esters **32**, **34**−**36**, **38**, and **39** to deliver the desired *δ*-lactones, we turned to *δ*-hydroxy carboxylic acids **17** and **18** as plausible lactone precursors. Interestingly, acid-induced esterification of 3,14-eupalmeroic acid (**17**) with catalytic amounts of PTSA·H_2O in refluxing benzene for 2 h resulted in the tricyclic *δ*-lactones **40** and **41** in 80% overall yield as a 3:1 mixture of isomers, respectively (eq 6). To our surprise, double



bond isomerization to the C-8 position was a major reaction pathway. On the other hand, our attempts to dehydrate 4,14-eupalmeroic acid (**18**) using a variety of solvents and protic acids at temperatures ranging from 25 to 80 °C failed to produced the desired α-methylene-*δ*-lactone **42** (eq 7). Furthermore, ditrifluoroacetate **43**



was the sole product (isolated in 44% yield) when **18** was treated with trifluoroacetic anhydride in benzene-d_6 at 25 °C in an attempt to obtain **42** upon dehydration.

Biological Studies. The compounds listed in Table 1 were tested in the NCI's 60 cell-line human tumor screen. The results with 14 representative cell-lines are shown. In comparative testing against these human tumor cell-lines, euniolide (**1**) and 12,13-bisepieupalmerin (**2**) exhibited IC_{50} values of 0.1−43 *μ*g/mL. Eupalmerin acetate (**3**) exhibited IC_{50} values from 0.3−16 *μ*g/mL. All the synthetic analogues screened in this bioassay were less toxic than their prototypes, suggesting that the present structural modifications were generally deleterious to the cytotoxicity of precursors **1**−**3**. Thus, analogues **5**, **8**, **12**,

Table 1. Comparison of in Vitro Cytotoxicities of Compounds 1, 2, and 3 with Those of Selected Analogues

	effects on human cancer cell growth IC_{50} (*μ*g/mL)[a]													
	leukemia		prostate carcinoma		melanoma		breast carcinoma		CNS carcinoma	ovarian carcinoma		colon carcinoma		lung carcinoma
compd	CCRF-CEM	MOLT-4	PC-3	DU-145	LOX-IMV1	MALME-3M	MCF7	MCF7 ADR-RES	SNB-75	IGROV1	OVCAR-3	HCT-116	COLO 205	NCI-H522
1	5	NT[b]	NT	NT	NT	NT	22	NT	NT	NT	NT	43	NT	NT
2	0.1	2	13	6	4	11	1	5	15	2	11	3	3	2
3	0.3	2	2	1	2	16	2	1	2	1	2	1	2	1
5	46	22	>100	>100	19	>100	41	>100	>100	42	>100	41	>100	32
8	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
12	33	57	>100	>100	41	>100	46	>100	>100	93	>100	64	>100	67
13	3	3	10	14	4	13	7	10	12	10	12	8	14	6
17	22	23	>100	>100	22	53	84	>100	>100	56	>100	69	70	23
19	>100	5	20	43	18	13	10	NT	45	24	15	16	7	4
27	22	25	40	84	30	61	27	33	75	37	37	53	33	18
28	>100	>100	>100	>100	>100	NT	>100	>100	>100	>100	>100	>100	>100	>100
30	14	>100	>100	>100	6	>100	>100	NT	>100	>100	>100	>100	>100	28
32	>100	26	32	67	61	>100	42	39	0.3	37	51	51	57	38
40	10	3	8	6	3	6	2	2	16	4	2	3	2	1

[a] The IC_{50} is the drug concentration that reduced cell number by 50%. [b] Not tested.

17, **19**, **27**, **28**, **30**, and **32** were nontoxic; several of the cell-lines gave IC_{50} values of 20−80 μg/mL, while others were not responsive at 100 μg/mL. On the other hand, α-methylene-δ-lactones **13** and **40** showed a characteristic pattern of differential cytotoxicity and were approximately equipotent (e.g., mean panel GI_{50}'s ∼ 1−16 nM). As a matter of interest, the eupalmerin acetate (**3**) isolated in this study was utilized in a Hollow Fiber Assay for in vivo antitumor activity.[12] Using a high dose of 40 mg/kg against 12 human tumor cell-lines implanted subcutaneously and intraperitoneally in athymic mice, we observed some activity against several of the cell-lines. While these data require confirmation, they are suggestive of in vivo antitumor activity. Further pharmacological evaluation of this series of nontoxic compounds in relevant in vitro tests is currently in progress.

Experimental Section

General Experimental Procedures. Infrared spectra were determined as thin films and were referenced to polystyrene. ^{1}H NMR, ^{13}C NMR, DEPT, HMQC, HMBC, ^{1}H−^{1}H COSY, RCT COSY, and 2D-NOESY spectra were recorded either at 300 and 500 MHz for ^{1}H or at 75 and 125 MHz for ^{13}C. Column chromatography was carried out with silica gel (35−75 mesh). HPLC was performed using a 10 μm silica gel Partisil 10 semipreparative column (9.4 mm × 50 cm) or a 10 μm Ultrasphere-CN semipreparative column (10 mm × 25 cm). Unless otherwise noted, ether and THF were freshly distilled from sodium wire and sodium benzophenone ketyl, respectively. Samples were photolyzed externally using a Xe (Hg) ozone free 1000 W UV lamp with a 7-51 Corning filter. Reactions were monitored by TLC on silica gel plates (0.25 mm) and visualized using UV light and I_2 vapors. Diazomethane was prepared *in-house*.[13] Reagents from commercial suppliers were used as provided. Yields refer to chromatographically and spectroscopically pure materials.

Extraction and Isolation of *Eunicea* γ-Cembranolides 1−3. The Caribbean gorgonian octocorals *E. succinea* and *E. mammosa* were collected at 25 m depth by SCUBA from Mona Island, Puerto Rico. The gorgonians were stored at 0 °C immediately after collection and then were frozen at −10 °C upon arrival, freeze-dried, and kept frozen until extraction. The dried *E. succinea* (2.5 kg) was blended with MeOH:$CHCl_3$ (1:1), and after filtration the crude extract was evaporated under vacuum to yield a residue (322.9 g) which was partitioned between hexane and H_2O. The hexane extract was concentrated to yield 170.9 g of a dark green oily residue, which was later dissolved in toluene and filtered. The resulting filtrate was concentrated (168.9 g), loaded onto a large size exclusion column (Bio-Beads SX-3), and eluted with toluene. The combined terpenoid-rich fractions (TLC guided) were concentrated to a dark yellow oil (118.6 g) and chromatographed over a large silica gel column (3 kg) using 30% EtOAc in hexane. From this column, 14 fractions were obtained, the less polar of which consisted of complex mixtures of unidentified sterols and fatty acid derivatives, and the known cembranolide diterpenes euniolide (**1**)[4] (24 g) and eupalmerin acetate (**3**)[6] (12.9 g). The more polar portion of the extract was divided roughly into fractions 6−14 on the basis of TLC analyses. From some of these fractions several known cembranolides were identified among which 12,13-bisepieupalmerin (**2**)[5] (5.0 g) stood out as the most abundant. The identification of **1**−**3** was accomplished through detailed comparisons with the physical and chemical data previously reported for these compounds. A similar extraction procedure was followed with the dried *E. mammosa* specimens.

(12) Hollingshead, M. G.; Alley, M. C.; Camalier, R. F.; Abbott, B. J.; Mayo, J. G.; Malspeis, L.; Grever, M. R. *Life Sci.* **1995**, *57*, 131−141.

(13) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.

Reaction of Euniolide (1) with Alkalies. Path A. A mixture of **1** (1.16 g, 0.0037 mol) and NaOH (1.14 g, 0.028 mol) in 50 mL of undistilled 1:1 MeOH/THF was stirred at 0 °C for 24 h before it was neutralized with 0.1 N HCl and then diluted with water (50 mL), extracted with CH_2Cl_2 (3 × 50 mL), and concentrated. The resulting oil was chromatographed on silica gel (85 g, 1:9 (v/v) ethyl acetate in hexane) to give 102 mg (13%) of eunioloic acid methyl ester (**4**), 97 mg (13%) of 15(*S*),17-epoxyeuniolide (**5**), 278 mg (35%) of a 2:1 mixture of **6** and **7**, and 437 mg of **1**. The mixture of **6** and **7** was separated by silica gel chromatography (10 g, elution with 10% ether in $CHCl_3$).

Data for 4: yellowish oil; $[\alpha]^{25}_D$ −15.9° (*c* 6.4, $CHCl_3$); IR (neat) 3430, 1718, 1626, 1258, 1148, 1073 cm^{-1}; UV (MeOH) λ_{max} 209 nm (ε 11700); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.86 (m, 1H, H-1), 1.79 (m, 1H, H-2), 2.07 (m, 1H, H-2′), 3.84 (t, 1H, *J* = 7.8 Hz, H-3), 1.71 (m, 2H, H-5), 2.07 (m, 2H, H-6), 5.24 (br t, 1H, *J* = 6.9 Hz, H-7), 2.12 (m, 2H, H-9), 2.15 (m, 2H, H-10), 5.03 (br t, 1H, *J* = 7.5 Hz, H-11), 1.73 (m, 1H, H-13), 2.30 (dd, 1H, *J* = 2.7, 14.1 Hz, H-13′), 3.90 (m, 1H, H-14), 5.64 (br s, 1H, H-17), 6.27 (br s, 1H, H-17′), 1.12 (s, 3H, Me-18), 1.52 (s, 3H, Me-19), 1.60 (s, 3H, Me-20), 3.77 (s, 3H, OC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.0 (d, C-1), 33.7 (t, C-2), 83.5 (d, C-3), 73.9 (s, C-4), 39.8 (t, C-5), 22.2 (t, C-6), 128.4 (d, C-7), 132.5 (s, C-8), 39.1 (t, C-9), 25.2 (t, C-10), 128.0 (d, C-11), 130.6 (s, C-12), 42.7 (t, C-13), 80.9 (d, C-14), 141.1 (s, C-15), 167.3 (s, C-16), 124.5 (t, C-17), 23.2 (q, C-18), 15.2 (q, C-19), 17.0 (q, C-20), 51.9 (q, O*C*H$_3$); HREI-MS *m*/*z* [M]$^+$ calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2292, 348 (7), 346 (8), 331 (13), 330 (50), 192 (87), 155 (100).

Data for 5: yellowish oil; $[\alpha]^{25}_D$ +9.5° (*c* 1.9, $CHCl_3$); IR (neat) 1790, 1262, 1105, 972 cm^{-1}; UV (MeOH) λ_{max} 209 nm (ε 4500); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.58 (m, 1H, H-1), 1.30 (ddd, 1H, *J* = 2.1, 5.1, 9.6 Hz, H-2), 2.03 (m, 1H, H-2′), 2.88 (dd, 1H, *J* = 4.2, 9.6 Hz, H-3), 1.48 (m, 1H, H-5), 1.92 (m, 1H, H-5′), 1.86 (m, 1H, H-6), 2.11 (m, 1H, H-6′), 4.94 (br t, 1H, *J* = 6.6 Hz, H-7), 1.97 (m, 1H, H-9), 2.16 (m 1H, H-9′), 2.06 (m, 1H, H-10), 2.32 (m, 1H, H-10′), 5.03 (m, 1H, H-11), 2.45 (br d, 1H, *J* = 10.2 Hz, H-13), 2.61 (m, 1H, H-13′), 5.03 (m, 1H, H-14), 3.03 (d, 1H, *J* = 5.1 Hz, H-17), 3.23 (d, 1H, *J* = 5.1 Hz, H-17′), 1.23 (s, 3H, Me-18), 1.56 (s, 3H, Me-19), 1.70 (s, 3H, Me-20); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.9 (d, C-1), 26.3 (t, C-2), 58.2 (d, C-3), 60.3 (s, C-4), 36.7 (t, C-5), 22.2 (t, C-6), 125.3 (d, C-7), 134.9 (s, C-8), 39.0 (t, C-9), 24.9 (t, C-10), 126.7 (d, C-11), 129.9 (s, C-12), 37.9 (t, C-13), 80.3 (d, C-14), 60.1 (s, C-15), 172.4 (s, C-16), 49.1 (t, C-17), 17.4 (q, C-18), 15.7 (q, C-19), 17.8 (q, C-20); HREI-MS *m*/*z* [M]$^+$ calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.2014, 332 (14), 318 (11), 133 (46), 119 (58), 107 (76), 93 (100).

Data for 6: yellowish oil; $[\alpha]^{25}_D$ −5.8° (*c* 7.6, $CHCl_3$); IR (neat) 1777, 1260, 1163, 1046 cm^{-1}; UV (MeOH) λ_{max} 209 nm (ε 4900); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (m, 1H, H-1), 1.71 (m, 1H, H-2), 1.81 (dd, 1H, *J* = 6.8, 9.9 Hz, H-2′), 2.91 (t, 1H, *J* = 6.7 Hz, H-3), 1.46 (m, 1H, H-5), 1.98 (m, 1H, H-5′), 1.94 (m, 1H, H-6), 2.17 (m, 1H, H-6′), 4.96 (br t, 1H, *J* = 7.2 Hz, H-7), 2.15 (m, 2H, H-9), 2.23 (m, 2H, H-10), 5.10 (m, 1H, H-11), 2.45 (d, 2H, *J* = 6.5 Hz, H-13), 4.78 (dd, 1H, *J* = 6.8, 13.3 Hz, H-14), 2.61 (dt, 1H, *J* = 3.7, 10.5 Hz, H-15), 3.63 (dd, 1H, *J* = 3.4, 9.8 Hz, H-17), 3.75 (dd, 1H, *J* = 4.0, 9.8 Hz, H-17′), 1.27 (s, 3H, Me-18), 1.57 (s, 3H, Me-19), 1.70 (s, 3H, Me-20), 3.34 (s, 3H, OC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.1 (d, C-1), 27.4 (t, C-2), 59.3 (d, C-3), 59.7 (s, C-4), 37.2 (t, C-5), 22.5 (t, C-6), 125.4 (d, C-7), 134.3 (s, C-8), 39.1 (t, C-9), 24.6 (t, C-10), 126.8 (d, C-11), 130.7 (s, C-12), 39.2 (t, C-13), 80.1 (d, C-14), 45.2 (d, C-15), 176.3 (s, C-16), 68.7 (t, C-17), 17.3 (q, C-18), 15.5 (q, C-19), 16.9 (q, C-20), 59.2 (q, O*C*H$_3$); HREI-MS *m*/*z* [M]$^+$ calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2327, 348 (12), 330 (5), 109 (86), 107 (75), 93 (85), 68 (100).

Data for 7: yellowish oil; $[\alpha]^{25}_D$ +18.9° (*c* 6.2, $CHCl_3$); IR (neat) 1771, 1260, 1176, 1098 cm^{-1}; UV (MeOH) λ_{max} 208 nm (ε 4700); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.67 (m, 1H, H-1), 1.31 (m, 1H, H-2), 1.80 (m, 1H, H-2′), 2.68 (m, 1H, H-3), 1.12 (m, 1H, H-5), 2.05 (m, 1H, H-5′), 2.37 (m, 2H, H-6), 4.87 (br d, 1H, *J* = 10.1 Hz, H-7), 2.03 (m, 2H, H-9), 1.96 (m, 1H, H-10), 2.38 (m, 1H, H-10′), 5.05 (br t, 1H, *J* = 6.7 Hz, H-11), 2.43 (m, 1H, H-13), 2.71 (m, 1H, H-13′), 4.75 (dt, 1H, *J* = 3.6, 12.0 Hz, H-14),

3.19 (m, 1H, H-15), 3.46 (t, 1H, J = 10.1 Hz, H-17), 3.77 (dd, 1H, J = 5.1, 10.1 Hz, H-17′), 1.27 (s, 3H, Me-18), 1.57 (s, 3H, Me-19), 1.64 (s, 3H, Me-20), 3.35 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.8 (d, C-1), 22.5 (t, C-2), 60.9 (d, C-3), 61.1 (s, C-4), 39.1 (t, C-5), 23.2 (t, C-6), 125.4 (d, C-7), 135.3 (s, C-8), 38.8 (t, C-9), 25.3 (t, C-10), 123.6 (d, C-11), 129.7 (s, C-12), 35.8 (t, C-13), 80.3 (d, C-14), 46.8 (d, C-15), 174.7 (s, C-16), 67.5 (t, C-17), 18.1 (q, C-18), 15.8 (q, C-19), 15.9 (q, C-20), 58.9 (q, OCH_3); HREI-MS m/z [M]$^+$ calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2294, 348 (26), 330 (14), 285 (5), 245 (10), 134 (42), 120 (48), 93 (91), 67 (100).

Path B. A suspension of **1** (325 mg, 1.03 mmol) in 3% aqueous KOH (50 mL) was stirred vigorously at 70 °C for 4 h, cooled to room temperature, neutralized with 0.1 N HCl, and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were dried and concentrated to leave a residue (369 mg) that was chromatographed on silica gel (15 g). Elution with 2% MeOH in $CHCl_3$ yielded 99 mg (29%) of eunioloic acid (**8**), 96 mg (28%) of isocrassin alcohol (**9**),[4b] and 71 mg (21%) of crassin alcohol (**10**).[8]

Data for eunioloic acid (8): colorless oil; $[\alpha]^{25}_D$ −18.8° (c 19.4, $CHCl_3$); IR (neat) 3600−3000 (broad), 1697, 1624, 1260, 1095, 1022 cm^{-1}; UV ($CHCl_3$) λ_{max} 244 nm (ϵ 750); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (m, 1H, H-1), 1.81 (dd, 1H, J = 7.8, 14.4 Hz, H-2), 2.12 (m, 1H, H-2′), 3.87 (br t, 1H, J = 7.8 Hz, H-3), 1.73 (br t, 2H, J = 6.0 Hz, H-5), 5.22 (t, 1H, J = 6.6 Hz, H-7), 5.03 (t, 1H, J = 6.9 Hz, H-11), 1.99 (dd, 1H, J = 8.4, 13.8 Hz, H-13), 2.28 (br d, 1H, J = 13.8 Hz, H-13′), 3.91 (m, 1H, H-14), 5.71 (br s, 1H, H-17), 6.39 (br s, 1H, H-17′), 1.13 (s, 3H, Me-18), 1.51 (s, 3H, Me-19), 1.59 (s, 3H, Me-20), 6.64 (br s, 1H, exchangeable, COOH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.7 (d, C-1), 33.6 (t, C-2), 83.3 (d, C-3), 74.4 (s, C-4), 40.0 (t, C-5), 22.2 (t, C-6), 128.2 (d, C-7), 132.4 (s, C-8), 39.1 (t, C-9), 25.1 (t, C-10), 127.9 (d, C-11), 130.5 (s, C-12), 42.7 (t, C-13), 80.8 (d, C-14), 140.6 (s, C-15), 171.1 (s, C-16), 126.3 (t, C-17), 22.8 (q, C-18), 15.1 (q, C-19), 16.9 (q, C-20); HREI-MS m/z [M]$^+$ calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2141, 334 (7), 316 (15), 298 (2), 192 (45), 109 (59), 81 (100).

Data for isocrassin alcohol (9): yellowish oil; $[\alpha]^{25}_D$ −0.12° (c 1.2, $CHCl_3$); IR (neat) 3467, 1763, 1662, 1274, 1165, 1090 cm^{-1}; UV ($CHCl_3$) λ_{max} 244 nm (ϵ 300); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.41 (m, 1H, H-1), 3.36 (m, 1H, H-3), 5.02 (br t, 1H, J = 6.5 Hz, H-7), 5.26 (m, 1H, H-11), 2.24 (dd, 1H J = 12.0, 16.0 Hz, H-13), 2.73 (br d, 1H, J = 16.0 Hz, H-13′), 4.79 (ddd, 1H, J = 4.0, 6.2, 12.0 Hz, H-14), 5.69 (d, 1H, J = 0.5 Hz, H-17), 6.28 (d, 1H, J = 0.7 Hz, H-17′), 1.06 (s, 3H, Me-18), 1.62 (s, 3H, Me-19), 1.70 (s, 3H, Me-20); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 38.3 (d, C-1), 27.6 (t, C-2), 74.8 (d, C-3), 73.9 (s, C-4), 38.3 (t, C-5), 21.7 (t, C-6), 127.0 (d, C-7), 135.2 (s, C-8), 38.4 (t, C-9), 24.4 (t, C-10), 127.5 (d, C-11), 129.5 (s, C-12), 38.7 (t, C-13), 78.2 (d, C-14), 138.8 (s, C-15), 170.1 (s, C-16), 123.2 (t, C-17), 28.1 (q, C-18), 16.3 (q, C-19), 17.0 (q, C-20); HREI-MS m/z [M]$^+$ calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2148, 334 (3), 316 (11), 298 (4), 107 (49), 93 (71), 81 (100).

Data for crassin alcohol (10): colorless oil; IR (neat) 3418, 1715, 1619, 1282, 1099, 1022 cm^{-1}; UV ($CHCl_3$) λ_{max} 248 nm (ϵ 800); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (m, 1H, H-1), 3.93 (d, 1H, J = 11.1 Hz, H-3), 5.05 (t, 1H, J = 7.5 Hz, H-7), 5.23 (m, 1H, H-11), 4.20 (ddd, 1H, J = 2.1, 5.1, 11.1 Hz, H-14), 5.70 (d, 1H, J = 1.5 Hz, H-17), 6.52 (d, 1H, J = 2.1 Hz, H-17′), 1.38 (s, 3H, Me-18), 1.58 (s, 3H, Me-19), 1.64 (s, 3H, Me-20), 2.48−1.60 (broad envelope, 12H), 2.68 (br s, 2H, exchangeable, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.2 (d, C-1), 19.2 (t, C-2), 82.6 (d, C-3), 74.0 (s, C-4), 38.7 (t, C-5), 22.1 (t, C-6), 125.3 (d, C-7), 135.3 (s, C-8), 40.1 (t, C-9), 24.0 (t, C-10), 127.5 (d, C-11), 130.7 (s, C-12), 44.6 (t, C-13), 71.8 (d, C-14), 138.4 (s, C-15), 168.1 (s, C-16), 127.6 (t, C-17), 24.6 (q, C-18), 14.5 (q, C-19), 14.9 (q, C-20); HREI-MS m/z [M]$^+$ calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2150, 334 (14), 316 (21), 291 (40), 109 (92), 93 (59), 68 (100).

Acetylation of Crassin Alcohol (10). A mixture of **10** (15 mg, 0.045 mmol), acetic anhydride (1 mL), and pyridine (2 mL) was stirred in CH_2Cl_2 (8 mL) at room temperature for 24 h, diluted with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were concentrated, leaving a residue that was subjected to chromatography (SiO_2, 10% ethyl acetate in hexane) to give 12 mg (71%) of known crassin acetate (**11**).[10]

Saponification of 12,13-Bisepieupalmerin (2) with Aqueous KOH. A suspension of **2** (619 mg, 1.85 mmol) in 3% aqueous KOH (15 mL) was stirred vigorously at 90−100 °C for 22 h and then cooled, diluted with water (50 mL), quenched with 5 N HCl, and extracted with chloroform (4 × 100 mL). The combined organic extracts were washed with saturated NaCl, dried, and concentrated. The crude white foam obtained (597 mg) was chromatographed on silica gel (24 g) using a 98:2:0.5 mixture of chloroform/MeOH/acetic acid as eluant to yield 413 mg (63%) of 12,13-bisepieupalmeroic acid (**12**).

Data for 12: white foam; $[\alpha]^{32}_D$ −11.6° (c 2.1, $CHCl_3$); IR (neat) 3596, 3580−3200 (broad), 1701, 1623, 1287, 1162, 1084, 1056 cm^{-1}; UV (MeOH) λ_{max} 208 (ϵ 9300) and 270 nm (ϵ 1700); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.32 (br d, 1H, J = 8.4 Hz, H-1), 3.96 (dd, 1H, J = 6.0, 10.2 Hz, H-3), 5.34 (t, 1H, J = 7.5 Hz, H-7), 3.18 (br d, 1H, J = 9.9 Hz, H-13), 3.70 (dd, 1H, J = 2.7, 9.6 Hz, H-14), 5.74 (br s, 1H, H-17), 6.38 (br s, 1H, H-17′), 1.07 (s, 3H, Me-18), 1.54 (s, 3H, Me-19), 0.78 (d, 3H, J = 6.6 Hz, Me-20), 5.42 (br s, exchangeable, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.3 (d, C-1), 31.3 (t, C-2), 86.4 (d, C-3), 73.2 (s, C-4), 36.3 (t, C-5), 21.6 (t, C-6), 129.2 (d, C-7), 132.1 (s, C-8), 37.4 (t, C-9), 21.2 (t, C-10), 32.2 (t, C-11), 30.5 (d, C-12), 79.0 (d, C-13), 84.6 (d, C-14), 141.8 (s, C-15), 170.7 (s, C-16), 125.5 (t, C-17), 25.7 (q, C-18), 14.7 (q, C-19), 10.9 (q, C-20); HREI-MS m/z [M]$^+$ calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2261, 352 (1), 334 (15), 316 (45), 298 (16), 95 (83), 55 (100).

δ-Lactonization of 12,13-Bisepieupalmeroic Acid (12). To a solution of **12** (48 mg, 0.13 mmol) in dry benzene (10 mL) was added glacial acetic acid (2 drops). The solution was heated to 65−70 °C for 120 h using a Dean−Stark apparatus, cooled, and concentrated, and the residue was subjected to silica gel chromatography (2.0 g, 30% ethyl acetate in hexane), giving 44 mg (98%) of 12,13-bisepieupalmerolide (**13**).

Data for 13: colorless oil; $[\alpha]^{32}_D$ −63.5° (c 1.15, $CHCl_3$); IR (neat) 3462 (sharp), 1712, 1638, 1263, 1238, 1149, 1099 cm^{-1}; UV (MeOH) λ_{max} 209 nm (ϵ 18500); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.56 (m, 1H, H-1), 1.88 (m, 1H, H-2), 2.17 (m, 1H, H-2′), 4.01 (dd, 1H, J = 1.0, 9.6 Hz, H-3), 5.26 (t, 1H, J = 7.6 Hz, H-7), 4.02 (dd, 1H, J = 6.3, 9.3 Hz, H-13), 3.18 (dd, 1H, J = 9.3, 11.1 Hz, H-14), 5.48 (dd, 1H, J = 0.7, 2.7 Hz, H-17), 6.38 (dd, 1H, J = 0.7, 3.0 Hz, H-17′), 1.15 (s, 3H, Me-18), 1.58 (s, 3H, Me-19), 1.12 (d, 3H, J = 6.7 Hz, Me-20); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 46.2 (d, C-1), 28.1 (t, C-2), 84.3 (d, C-3), 73.3 (s, C-4), 41.3 (t, C-5), 21.4 (t, C-6), 126.9 (d, C-7), 133.2 (s, C-8), 36.9 (t, C-9), 24.7 (t, C-10), 28.4 (t, C-11), 38.7 (d, C-12), 86.4 (d, C-13), 81.1 (d, C-14), 136.8 (s, C-15), 164.4 (s, C-16), 124.6 (t, C-17), 23.2 (q, C-18), 16.6 (q, C-19), 17.5 (q, C-20); HREI-MS m/z [M]$^+$ calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2151, 334 (7), 316 (25), 208 (13), 164 (29), 109 (34), 93 (61), 81 (91), 55 (100).

Treatment of 12,13-Bisepieupalmeroic acid (12) with Diazomethane Followed by the Thermolysis of Pyrazolines 14a,b. A solution of diazomethane in ether (30 mL) was added to a solution of **12** (94 mg, 0.27 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 30 min prior to being concentrated and stored under high vacuum. The resulting oil (108 mg, 100%), which consisted of a 1:1.5 epimeric mixture of two pyrazolines as established by TLC and NMR spectroscopic analyses, was used in the next step without further purification. HREI-MS (crude mixture of epimers) m/z [M]$^+$ calcd for $C_{22}H_{36}N_2O_5$ 408.2624, found 408.2619, 408 (11), 380 (7), 362 (52), 331 (16), 209 (25), 195 (37), 169 (100), 123 (64), 109 (76), 95 (90), 81 (93). A solution of pyrazolines **14a**,**b** (110 mg, 0.27 mmol) in toluene (30 mL) was treated with glacial acetic acid (10 mL), warmed to 110−120 °C for 4.5 h, cooled, and concentrated to leave a crude oil that was purified by means of silica gel chromatography (4.3 g, eluted with 25% ethyl acetate in hexane), giving 17 mg (19%) of δ-lactone **15** and 30 mg (32%) of δ-lactone **16**.

Data for 15: colorless oil; $[\alpha]^{29}_D$ −66.0° (c 1.0, $CHCl_3$); IR (neat) 3448, 1726, 1710, 1141, 1096, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (m, 1H, H-1), 3.96 (dd, 1H, J = 5.1, 9.3 Hz, H-3), 2.15 (m, 2H, H-6), 5.26 (br t, 1H, J = 7.2 Hz,

H-7), 4.04 (dd, 1H, J = 9.6, 9.9 Hz, H-13), 3.35 (dd, 1H, J = 9.3, 9.9 Hz, H-14), 1.10 (m, 2H, H-17), 1.11 (s, 3H, Me-18), 1.58 (s, 3H, Me-19), 1.10 (d, 3H, J = 6.9 Hz, Me-20), 0.73 (m, 1H, H-21), 1.52 (m, 1H, H-21′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.3 (d, C-1), 24.8 (t, C-2), 84.0 (d, C-3), 73.3 (s, C-4), 41.1 (t, C-5), 21.4 (t, C-6), 126.8 (d, C-7), 133.3 (s, C-8), 36.9 (t, C-9), 26.2 (t, C-10), 28.5 (t, C-11), 38.7 (d, C-12), 86.4 (d, C-13), 80.9 (d, C-14), 23.1 (s, C-15), 174.2 (s, C-16), 13.8 (t, C-17), 23.3 (q, C-18), 16.8 (q, C-19), 17.6 (q, C-20), 13.1 (t, C-21); HREI-MS m/z $[M]^+$ calcd for $C_{21}H_{32}O_4$ 348.2300, found 348.2290, 348 (49), 330 (31), 236 (20), 155 (74), 109 (79), 95 (93), 81 (96), 55 (100).

Data for 16: colorless oil; $[\alpha]^{29}_D$ −1.9° (c 1.6, $CHCl_3$); IR (neat) 3443, 1720, 1638, 1214, 1135, 1091 cm^{-1}; UV (MeOH) λ_{max} 220 nm (ϵ 6200); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.52 (m, 1H, H-1), 3.99 (dd, 1H, J = 4.5, 9.3 Hz, H-3), 5.25 (br t, 1H, J = 7.5 Hz, H-7), 3.94 (dd, 1H, J = 9.6, 9.9 Hz, H-13), 3.17 (dd, 1H, J = 9.3, 9.6 Hz, H-14), 6.10 (dq, 1H, J = 2.7, 7.5 Hz, H-17), 1.13 (s, 3H, Me-18), 1.58 (s, 3H, Me-19), 1.11 (d, 3H, J = 6.6 Hz, Me-20), 2.17 (dd, 3H, J = 2.7, 7.5 Hz, Me-21); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 47.2 (d, C-1), 28.1 (t, C-2), 84.0 (d, C-3), 73.3 (s, C-4), 41.2 (t, C-5), 21.4 (t, C-6), 126.8 (d, C-7), 133.2 (s, C-8), 36.9 (t, C-9), 25.2 (t, C-10), 28.6 (t, C-11), 39.0 (d, C-12), 85.8 (d, C-13), 81.4 (d, C-14), 127.9 (s, C-15), 163.9 (s, C-16), 140.0 (d, C-17), 23.2 (q, C-18), 16.9 (q, C-19), 17.8 (q, C-20), 15.7 (q, C-21); HREI-MS m/z $[M]^+$ calcd for $C_{21}H_{32}O_4$ 348.2300, found 348.2294, 348 (56), 330 (43), 256 (18), 178 (46), 109 (76), 81 (88), 55 (100).

Saponification of Eupalmerin Acetate (3) with Aqueous KOH. **Path A.** A suspension of **3** (2.03 g, 5.41 mmol) in 3% aqueous KOH (40 mL) was stirred vigorously at 70 °C for 18 h and then cooled, diluted with water (125 mL), quenched with 5 N HCl, and extracted with $CHCl_3$ (3 × 125 mL). The combined organic extracts were washed with saturated NaCl, dried, and concentrated. The foam obtained (1.67 g) was chromatographed on a silica gel column (70 g) eluted with a 97:3:0.5 mixture of chloroform/MeOH/acetic acid to yield 390 mg (21%) of 3,14-eupalmeroic acid (**17**), 308 mg (16%) of 4,14-eupalmeroic acid (**18**), 91 mg (5%) of eucrassin alcohol (**19**), and 28 mg (2%) of isoeucrassin alcohol (**20**).

Data for 17: colorless oil; $[\alpha]^{21}_D$ −36.3° (c 1.3, $CHCl_3$); IR (neat) 3630−3075 (broad), 1767, 1208, 1165, 1093 cm^{-1}; UV (MeOH) λ_{max} 210 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.14 (m, 1H, H-1), 3.86 (t, 1H, J = 7.5 Hz, H-3), 5.19 (br s, 1H, H-7), 3.03 (d, 1H, J = 9.3 Hz, H-13), 3.70 (d, 1H, J = 9.3 Hz, H-14), 5.76 (br s, 1H, H-17), 6.38 (br s, 1H, H-17′), 1.16 (s, 3H, Me-18), 1.53 (s, 3H, Me-19), 0.98 (d, 3H, J = 6.3 Hz, Me-20), 4.53 (br s, exchangeable, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.9 (d, C-1), 33.2 (t, C-2), 80.7 (d, C-3), 74.1 (s, C-4), 39.4 (t, C-5), 21.9 (t, C-6), 131.7 (d, C-7), 127.3 (s, C-8), 42.7 (t, C-9), 22.4 (t, C-10), 30.0 (t, C-11), 37.0 (d, C-12), 73.8 (d, C-13), 83.4 (d, C-14), 139.4 (s, C-15), 170.9 (s, C-16), 128.6 (t, C-17), 21.7 (q, C-18), 15.6 (q, C-19), 16.7 (q, C-20); HREI-MS m/z $[M]^+$ calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2235, 352 (5), 334 (21), 316 (9), 193 (22), 141 (45), 109 (40), 95 (82), 81 (100).

Data for 18: colorless oil; IR (neat) 3620−3045 (broad), 1763, 1448, 1158, 1066, 1037 cm^{-1}; UV (MeOH) λ_{max} 210 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.17 (m, 1H, H-1), 3.37 (br s, 1H, H-3), 5.49 (br t, 1H, J = 9.3 Hz, H-7), 2.87 (d, 1H, J = 10.5 Hz, H-13), 4.02 (br d, 1H, J = 10.5 Hz, H-14), 5.63 (br s, 1H, H-17), 6.33 (br s, 1H, H-17′), 1.32 (s, 3H, Me-18), 1.56 (s, 3H, Me-19), 0.87 (d, 3H, J = 6.3 Hz, Me-20), 4.79 (br s, exchangeable, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.9 (d, C-1), 33.3 (t, C-2), 71.5 (d, C-3), 77.6 (s, C-4), 31.0 (t, C-5), 23.1 (t, C-6), 126.3 (d, C-7), 131.6 (s, C-8), 36.4 (t, C-9), 20.6 (t, C-10), 29.0 (t, C-11), 29.5 (d, C-12), 75.1 (d, C-13), 70.0 (d, C-14), 141.6 (s, C-15), 170.0 (s, C-16), 127.8 (t, C-17), 20.9 (q, C-18), 13.7 (q, C-19), 15.1 (q, C-20); HREI-MS m/z $[M]^+$ calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2245, 352 (60), 334 (25), 316 (9), 184 (11), 181 (12), 121 (28), 95 (81), 81 (100).

Data for 19: colorless oil; $[\alpha]^{21}_D$ +49.4° (c 3.4, $CHCl_3$); IR (neat) 3411, 1708, 1620, 1262, 1179, 1101, 1028 cm^{-1}; UV (MeOH) λ_{max} 210 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.71 (m, 1H, H-1), 4.11 (d, 1H, J = 10.5 Hz, H-3), 5.13 (br t, 1H, J = 7.5 Hz, H-7), 3.43 (d, 1H, J = 8.7 Hz, H-13), 3.97 (br d, 1H, J = 8.7 Hz, H-14), 5.81 (br s, 1H, H-17), 6.71 (br d, 1H, J = 2.1 Hz, H-17′), 1.41 (s, 3H, Me-18), 1.59 (s, 3H, Me-19), 0.86 (d, 3H, J = 6.6 Hz, Me-20), 3.08 (br s, exchangeable, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.6 (d, C-1), 21.0 (t, C-2), 83.3 (d, C-3), 74.2 (s, C-4), 36.6 (t, C-5), 22.3 (t, C-6), 125.1 (d, C-7), 137.1 (s, C-8), 39.0 (t, C-9), 20.9 (t, C-10), 32.2 (t, C-11), 28.7 (d, C-12), 77.2 (d, C-13), 72.7 (d, C-14), 135.2 (s, C-15), 166.7 (s, C-16), 128.4 (t, C-17), 24.5 (q, C-18), 14.3 (q, C-19), 10.7 (q, C-20); HREI-MS m/z $[M]^+$ calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2249, 352 (12), 334 (11), 316 (9), 288 (4), 236 (6), 109 (44), 95 (83), 81 (100).

Data for 20: colorless oil; $[\alpha]^{21}_D$ +10.6° (c 1.7, $CHCl_3$); IR (neat) 3443, 1756, 1274, 1159, 1085, 1006 cm^{-1}; UV (MeOH) λ_{max} 210 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.41 (m, 1H, H-1), 3.46 (d, 1H, J = 11.1 Hz, H-3), 5.75 (br t, 1H, J = 7.5 Hz, H-7), 3.62 (d, 1H, J = 10.2 Hz, H-13), 4.42 (dd, 1H, J = 5.5, 10.2 Hz, H-14), 5.71 (br s, 1H, H-17), 6.29 (br s, 1H, H-17′), 1.06 (s, 3H, Me-18), 1.57 (s, 3H, Me-19), 0.88 (d, 3H, J = 6.6 Hz, Me-20), 2.86 (br s, 1H, exchangeable, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.0 (d, C-1), 27.7 (t, C-2), 73.5 (d, C-3), 74.6 (s, C-4), 39.2 (t, C-5), 21.5 (t, C-6), 128.6 (d, C-7), 134.2 (s, C-8), 35.8 (t, C-9), 20.4 (t, C-10), 30.9 (t, C-11), 28.3 (d, C-12), 74.4 (d, C-13), 82.1 (d, C-14), 138.6 (s, C-15), 169.8 (s, C-16), 123.5 (t, C-17), 28.7 (q, C-18), 14.1 (q, C-19), 10.1 (q, C-20); HREI-MS m/z $[M - H_2O]^+$ calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2134, 334 (12), 316 (7), 248 (6), 181 (10), 107 (42), 95 (77), 81 (96), 55 (100).

Path B. A suspension of **3** (3.50 g, 9.31 mmol) in 3% aqueous KOH (100 mL) was stirred vigorously at 70 °C for 2 h and then cooled, quenched with 5 N HCl, and extracted with chloroform (3 × 150 mL). The combined organic extracts were washed with saturated NaCl, dried, and concentrated to leave a white solid residue (3.54 g) that was used without further purification. Chloroform (50 mL) and a solution of diazomethane in ether (50 mL) were added. The solution was stirred at room temperature for 15 min prior to being concentrated and stored under high vacuum. Silica gel chromatography (95 g) eluting with 20% ethyl acetate in hexane followed by normal-phase HPLC (Partisil-10, elution with 1:1 (v/v) 2-propanol in hexane) provided 956 mg (27%) of **21**, 570 mg (16%) of **22**, 393 mg (10%) of **23**, 268 mg (8%) of **24**, and 893 mg (24%) of **25**.

Data for 21: light yellow oil; $[\alpha]^{21}_D$ −160.1° (c 6.0, $CHCl_3$); IR (neat) 3477, 1764, 1284, 1216, 1143, 1074, 1005 cm^{-1}; UV (MeOH) λ_{max} 206 and 320 (sh) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25 (m, 1H, H-1), 2.85 (dd, 1H, J = 5.4, 8.1 Hz, H-3), 5.05 (br t, 1H, J = 5.8 Hz, H-7), 3.61 (br d, 1H, J = 7.5 Hz, H-13), 4.99 (dd, 1H, J = 2.1, 7.5 Hz, H-14), 1.24 (s, 3H, Me-18), 1.64 (s, 3H, Me-19), 1.03 (d, 3H, J = 6.9 Hz, Me-20), 4.65 (br t, 2H, J = 7.6 Hz, H-21); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.9 (d, C-1), 25.4 (t, C-2), 58.8 (d, C-3), 60.2 (s, C-4), 38.3 (t, C-5), 23.2 (t, C-6), 126.0 (d, C-7), 135.3 (s, C-8), 38.0 (t, C-9), 23.7 (t, C-10), 31.6 (t, C-11), 34.9 (d, C-12), 73.0 (d, C-13), 80.1 (d, C-14), 97.6 (s, C-15), 174.0 (s, C-16), 23.2 (t, C-17), 16.3 (q, C-18), 16.2 (q, C-19), 16.5 (q, C-20), 78.4 (t, C-21); HREI-MS m/z $[M]^+$ calcd for $C_{21}H_{32}N_2O_4$ 376.2362, found 376.2414, 376 (1), 348 (7), 330 (11), 121 (45), 107 (49), 95 (57), 55 (100).

Data for 22: light yellow oil; $[\alpha]^{21}_D$ +50.7° (c 32.4, $CHCl_3$); IR (neat) 3421, 1777, 1338, 1218, 1143, 1072 cm^{-1}; UV ($CHCl_3$) λ_{max} 244 (ϵ 700) and 326 nm (ϵ 300); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.65 (m, 1H, H-1), 2.86 (dd, 1H, J = 5.1, 8.8 Hz, H-3), 5.04 (br t, 1H, J = 6.4 Hz, H-7), 3.70 (d, 1H, J = 8.7 Hz, H-13), 4.86 (d, 1H, J = 8.7 Hz, H-14), 1.24 (s, 3H, Me-18), 1.58 (s, 3H, Me-19), 1.07 (d, 3H, J = 6.9 Hz, Me-20), 4.67 (m, 1H, H-21), 4.83 (m, 1H, H-21′), 4.36 (br s, 1H, exchangeable, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.9 (d, C-1), 23.9 (t, C-2), 58.1 (d, C-3), 59.7 (s, C-4), 37.7 (t, C-5), 22.7 (t, C-6), 125.9 (d, C-7), 134.6 (s, C-8), 37.3 (t, C-9), 23.1 (t, C-10), 31.3 (t, C-11), 35.0 (d, C-12), 71.6 (d, C-13), 80.4 (d, C-14), 95.3 (s, C-15), 172.0 (s, C-16), 25.0 (t, C-17), 16.2 (q, C-18), 15.6 (q, C-19), 16.5 (q, C-20), 77.9 (t, C-21); HREI-MS m/z $[M]^+$ calcd for $C_{21}H_{32}N_2O_4$ 376.2362, found 376.2359, 376 (6), 348 (3), 330 (3), 195 (9), 177 (16), 95 (62), 81 (100).

Data for 23: light yellow oil; $[\alpha]^{25}_D$ −55.4° (c 7.4, $CHCl_3$); IR (neat) 3396, 1730, 1554, 1228, 1071 cm^{-1}; UV ($CHCl_3$) λ_{max} 244 and 330 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.95 (m, 1H,

H-1), 3.35 (br t, 1H, J = 2.7 Hz, H-3), 5.48 (m, 1H, H-7), 3.41 (d, 1H, J = 10.2 Hz, H-13), 3.89 (d, 1H, J = 10.5 Hz, H-14), 1.31 (s, 3H, Me-18), 1.55 (s, 3H, Me-19), 0.91 (d, 3H, J = 6.6 Hz, Me-20), 4.16 (m, 1H, H-21), 4.79 (ddd, 1H, J = 2.1, 9.3, 17.7 Hz, H-21′), 3.70 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.0 (d, C-1), 28.2 (t, C-2), 71.5 (d, C-3), 77.0 (s, C-4), 31.1 (t, C-5), 23.1 (t, C-6), 126.2 (d, C-7), 131.6 (s, C-8), 36.4 (t, C-9), 20.6 (t, C-10), 29.2 (t, C-11), 29.6 (d, C-12), 75.5 (d, C-13), 69.3 (d, C-14), 100.0 (s, C-15), 170.2 (s, C-16), 24.7 (t, C-17), 20.7 (q, C-18), 13.8 (q, C-19), 15.1 (q, C-20), 76.4 (t, C-21), 52.7 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{36}N_2O_5$ 408.2624, found 408.2637, 408 (1), 380 (58), 362 (29), 344 (9), 330 (8), 196 (38), 81 (100).

Data for 24: light yellow oil; $[\alpha]^{25}_D$ +60.8° (c 7.4, $CHCl_3$); IR (neat) 3396, 1732, 1558, 1223, 1070, 1051 cm^{-1}; UV ($CHCl_3$) λ_{max} 244 and 330 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.72 (m, 1H, H-1), 3.39 (br t, 1H, J = 3.0 Hz, H-3), 5.44 (m, 1H, H-7), 2.94 (d, 1H, J = 10.2 Hz, H-13), 3.95 (d, 1H, J = 10.5 Hz, H-14), 1.28 (s, 3H, Me-18), 1.57 (s, 3H, Me-19), 0.90 (d, 3H, J = 6.6 Hz, Me-20), 4.50 (ddd, 1H, J = 6.6, 9.3, 18.3 Hz, H-21), 4.63 (ddd, 1H, J = 5.4, 9.6, 18.3 Hz, H-21′), 3.77 (s, 3H, $-CO_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.3 (d, C-1), 29.1 (t, C-2), 71.5 (d, C-3), 78.0 (s, C-4), 31.2 (t, C-5), 23.1 (t, C-6), 126.1 (d, C-7), 131.8 (s, C-8), 36.4 (t, C-9), 20.5 (t, C-10), 29.0 (t, C-11), 29.8 (d, C-12), 75.2 (d, C-13), 68.6 (d, C-14), 100.1 (s, C-15), 169.8 (s, C-16), 26.3 (t, C-17), 20.7 (q, C-18), 13.8 (q, C-19), 15.0 (q, C-20), 77.2 (t, C-21), 52.7 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{36}N_2O_5$ 408.2624, found 408.2558, 408 (1), 380 (53), 362 (24), 344 (6), 196 (33), 152 (27), 95 (68), 55 (100).

Data for 25: light yellow oil; $[\alpha]^{25}_D$ −94.5° (c 30.3, $CHCl_3$); IR (neat) 3400, 1733, 1558, 1249, 1123, 1070 cm^{-1}; UV ($CHCl_3$) λ_{max} 244 (ϵ 350) and 326 nm (ϵ 300); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.01 (m, 1H, H-1), 3.64 (t, 1H, J = 8.1 Hz, H-3), 5.11 (t, 1H, J = 5.4 Hz, H-7), 3.07 (m, 1H, H-13), 3.73 (d, 1H, J = 8.4 Hz, H-14), 1.09 (s, 3H, Me-18), 1.47 (s, 3H, Me-19), 0.94 (d, 3H, J = 6.3 Hz, Me-20), 4.46 (m, 1H, H-21), 4.67 (ddd, 1H, J = 4.8, 10.2, 18.0 Hz, H-21′), 3.72 (s, 3H, $-CO_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.6 (d, C-1), 29.7 (t, C-2), 81.1 (d, C-3), 73.1 (s, C-4), 39.5 (t, C-5), 22.0 (t, C-6), 128.2 (d, C-7), 131.3 (s, C-8), 42.8 (t, C-9), 21.9 (t, C-10), 30.3 (t, C-11), 36.8 (d, C-12), 74.9 (d, C-13), 79.7 (d, C-14), 99.9 (s, C-15), 170.2 (s, C-16), 24.4 (t, C-17), 21.0 (q, C-18), 15.2 (q, C-19), 16.5 (q, C-20), 77.2 (t, C-21), 52.4 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{36}N_2O_5$ 408.2624, found 408.2609, 408 (1), 390 (1), 380 (1), 362 (5), 85 (66), 83 (100).

Path C. A suspension of **3** (106 mg, 0.28 mmol) in 3% aqueous KOH (28 mL) was stirred vigorously at 45 °C for 12 h and then cooled, quenched with 5 N HCl, and extracted with ether (3 × 30 mL). The combined organic extracts were washed with saturated NaCl, dried, and concentrated to leave a residue that was used without further purification. Pyridine (25 mL) and acetic anhydride (25 mL) were added, and the solution was stirred at room temperature for 1.5 h prior to being concentrated. Purification by silica gel chromatography (13 g) eluting with 40% ethyl acetate in hexane followed by normal-phase HPLC (Partisil-10, elution with 1:4 (v/v) 2-propanol in hexane) provided 18 mg (20%) of eupalmerolide (**26**) and 22 mg (20%) of acetate **27**. An undetermined amount of starting material **3** was also recovered.

Data for 26: colorless oil; IR (neat) 3450, 1722, 1642, 1260, 1130, 1094 cm^{-1}; UV (MeOH) λ_{max} 210 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.86 (m, 1H, H-1), 4.03 (dd, 1H, J = 4.6, 9.7 Hz, H-3), 5.19 (br t, 1H, J = 7.2 Hz, H-7), 4.37 (dd, 1H, J = 5.7, 10.5 Hz, H-13), 3.85 (dd, 1H, J = 5.4, 12.0 Hz, H-14), 5.49 (d, 1H, J = 2.1 Hz, H-17), 6.43 (d, 1H, J = 2.4 Hz, H-17′), 1.16 (s, 3H, Me-18), 1.59 (s, 3H, Me-19), 1.10 (d, 3H, J = 6.3 Hz, Me-20); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.7 (d, C-1), 29.4 (t, C-2), 88.4 (d, C-3), 72.9 (s, C-4), 36.6 (t, C-5), 22.3 (t, C-6), 128.4 (d, C-7), 133.3 (s, C-8), 37.6 (t, C-9), 23.3 (t, C-10), 29.2 (t, C-11), 35.9 (d, C-12), 84.1 (d, C-13), 78.7 (d, C-14), 136.9 (s, C-15), 163.8 (s, C-16), 126.0 (t, C-17), 25.8 (q, C-18), 16.5 (q, C-19), 15.7 (q, C-20); HRFAB-MS m/z [M + Na]$^+$ calcd for $C_{20}H_{30}O_4$Na 357.2042, found 357.2039; HREI-MS m/z [M−H_2O]$^+$ calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2045, 316 (21), 167 (24), 95 (76), 81 (100).

Data for 27: colorless oil; IR (neat) 3650−3039 (broad), 1721, 1712, 1240, 1073, 1025 cm^{-1}; UV (MeOH) λ_{max} 208 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.79 (m, 1H, H-1), 3.86 (br t, 1H, J = 7.6 Hz, H-3), 5.27 (br t, 1H, J = 5.7 Hz, H-7), 4.64 (dd, 1H, J = 1.8, 9.6 Hz, H-13), 3.98 (dd, 1H, J = 2.1, 9.0 Hz, H-14), 5.68 (br s, 1H, H-17), 6.37 (br s, 1H, H-17′), 1.18 (s, 3H, Me-18), 1.55 (s, 3H, Me-19), 0.82 (d, 3H, J = 6.6 Hz, Me-20), 2.09 (s, 3H, OCOCH_3), 3.20 (br s, exchangeable, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.6 (d, C-1), 34.2 (t, C-2), 81.4 (d, C-3), 74.0 (s, C-4), 39.4 (t, C-5), 22.4 (t, C-6), 128.4 (d, C-7), 131.8 (s, C-8), 42.1 (t, C-9), 25.3 (t, C-10), 30.3 (t, C-11), 34.8 (d, C-12), 75.4 (d, C-13), 81.3 (d, C-14), 139.3 (s, C-15), 170.1 (s, C-16), 127.5 (t, C-17), 22.1 (q, C-18), 15.7 (q, C-19), 16.2 (q, C-20), 171.0 (s, C-21), 20.9 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{34}O_6$ 394.2355, found 394.2355, 394 (4), 376 (25), 335 (12), 334 (51), 316 (30), 81 (100).

Path D. A suspension of **3** (1.05 g, 2.79 mmol) in 3% aqueous KOH (26 mL) was stirred vigorously at 45 °C for 18 h and then cooled, diluted with water (50 mL), quenched with 5 N HCl, and extracted with ether (3 × 75 mL). The combined organic extracts were washed with saturated NaCl, dried, and concentrated. A cooled solution (−78 °C) of the foam obtained (843 mg) in ethyl acetate (40 mL) was treated with O_3 until the solution turned light blue. The reaction was warmed to 20 °C, concentrated, diluted with water (40 mL), and treated with 30% hydrogen peroxide (5 drops). The solution was refluxed for 18 h and then cooled and concentrated to afford the crude product as a viscous oil that was purified by normal-phase HPLC (Ultrasphere-CN, elution with 15% 2-propanol in hexane) to provide 288 mg (30%) of carboxylic acid **28** and 552 mg (54%) of dicarboxylic acid **29**. Since **29** was sparingly soluble in $CDCl_3$ it was dissolved in a 1:1 mixture of chloroform and MeOH (10 mL), treated with 20 mL of diazomethane solution in ether, and concentrated to give 564 mg (96%) of diester **31** as an oil that was analyzed without further purification. After being treated with 10 mL of diazomethane solution in ether and stirred at room temperature for 30 min, carboxylic acid **28** (90 mg, 0.25 mmol) was layered on top of a 10 × 10 cm plug of silica gel (12 g) in a sintered glass frit, and 100 mL of 30% ethyl acetate in hexane was poured through under aspirator vacuum. Concentration of the filtrate afforded pure **30** (84 mg, 90%).

Data for 28: colorless oil; $[\alpha]^{21}_D$ −26.9° (c 7.2, $CHCl_3$); IR (neat) 3790−3050 (broad), 1770, 1734, 1713, 1261, 1171 cm^{-1}; UV (MeOH) λ_{max} 210 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.08 (m, 1H, H-1), 1.89 (m, 1H, H-2), 2.25 (m, 1H, H-2′), 4.05 (dd, 1H, J = 7.0, 8.8 Hz, H-3), 1.89 (m, 1H, H-5), 2.25 (m, 1H, H-5′), 2.61 (m, 2H, H-6), 2.41 (br t, 2H, J = 7.2 Hz, H-9), 3.45 (m, 1H, H-13), 4.14 (dd, 1H, J = 3.1, 6.1 Hz, H-14), 1.38 (s, 3H, Me-18), 2.12 (s, 3H, Me-19), 0.93 (d, 3H, J = 6.6 Hz, Me-20); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.4 (d, C-1), 28.8 (t, C-2), 83.4 (d, C-3), 86.7 (s, C-4), 30.2 (t, C-5), 29.0 (t, C-6), 176.9 (s, C-7), 210.1 (s, C-8), 43.6 (t, C-9), 21.0 (t, C-10), 32.7 (t, C-11), 36.3 (d, C-12), 75.4 (d, C-13), 82.6 (d, C-14), 176.9 (s, C-15), 23.6 (q, C-18), 29.9 (q, C-19), 14.6 (q, C-20); HRFAB-MS m/z [M + Na]$^+$ calcd for $C_{18}H_{28}O_7$Na 379.1733, found 379.1724; HREI-MS m/z [M−H_2O]$^+$ calcd for $C_{18}H_{26}O_6$ 338.1729, found 338.1738, 338 (8), 320 (3), 221 (25), 143 (34), 126 (43), 99 (100).

Data for 30: colorless oil; $[\alpha]^{21}_D$ −36.0° (c 1.2, $CHCl_3$); IR (neat) 3340, 1774, 1737, 1261, 1159, 1118, 1069 cm^{-1}; UV (MeOH) λ_{max} 206 nm (ϵ 1700); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (m, 1H, H-1), 4.19 (t, 1H, J = 7.6 Hz, H-3), 2.64 (br t, 2H, J = 9.6 Hz, H-6), 1.85 (m, 1H, H-12), 3.76 (br d, 1H, J = 9.9 Hz, H-13), 4.29 (t, 1H, J = 8.4 Hz, H-14), 1.40 (s, 3H, Me-18), 1.46 (s, 3H, Me-19), 0.88 (d, 3H, J = 6.9 Hz, Me-20), 3.73 (s, 3H, CO_2CH_3), 9.92 (br s, 1H, exchangeable, OH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.8 (d, C-1), 32.3 (t, C-2), 82.5 (d, C-3), 84.4 (s, C-4), 29.7 (t, C-5), 28.2 (t, C-6), 175.9 (s, C-7), 107.6 (s, C-8), 36.5 (t, C-9), 18.3 (t, C-10), 37.4 (t, C-11), 31.9 (d, C-12), 76.3 (d, C-13), 85.6 (d, C-14), 173.3 (s, C-15), 21.8 (q, C-18), 23.1 (q, C-19), 12.4 (q, C-20), 52.4 (q, CO_2CH_3); HREI-MS m/z [M − OH]$^+$ calcd for $C_{19}H_{29}O_6$ 353.1964, found 353.1951, 353 (9), 321 (45), 267 (14), 195 (58), 125 (69), 99 (100).

Data for 31: colorless oil; IR (neat) 3440, 1773, 1732, 1716, 1260, 1197, 1082, 1035 cm^{-1}; UV (MeOH) λ_{max} 210 nm; ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 3.10 (m, 1H, H-1), 1.61 (m, 1H, H-2), 2.10 (m, 1H, H-2′), 3.45 (m, 1H, H-3), 2.05 (m, 2H, H-5), 2.37 (m, 2H, H-6), 3.08 (m, 1H, H-13), 3.83 (br d, 1H, J = 10.5 Hz, H-14), 1.13 (s, 3H, Me-18), 2.09 (s, 3H, Me-19), 0.94 (d, 3H, J = 6.6 Hz, Me-20), 3.65 (s, 3H, CO_2CH_3), 3.63 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.9 (d, C-1), 28.4 (t, C-2), 68.1 (d, C-3), 76.0 (s, C-4), 30.5 (t, C-5), 28.1 (t, C-6), 174.5 (s, C-7), 208.9 (s, C-8), 43.8 (t, C-9), 21.0 (t, C-10), 32.8 (t, C-11), 35.6 (d, C-12), 75.0 (d, C-13), 69.9 (d, C-14), 173.7 (s, C-15), 21.5 (q, C-18), 29.7 (q, C-19), 15.2 (q, C-20), 51.7 (q, CO_2CH_3), 51.6 (q, CO_2CH_3); HREI-MS m/z [M − CH_3OH − OH]$^+$ calcd for $C_{19}H_{29}O_6$ 353.1964, found 353.1975, 353 (3), 321 (17), 309 (8), 209 (32), 195 (73), 125 (53), 99 (100).

Photolysis of Pyrazoline 23. A magnetically stirred solution of **23** (50 mg, 0.12 mmol) in 10% ethyl acetate in hexane (5 mL) placed in a small Pyrex test tube was irradiated for 2.5 h at 25 °C. After concentration, the resulting oil was chromatographed on silica gel (2 g, 30% ethyl acetate in hexane) to provide 47 mg (100%) of **32**.

Data for 32: colorless oil; $[\alpha]^{25}_D$ +13.4° (*c* 9.3, $CHCl_3$); IR (neat) 3401, 1718, 1226, 1193, 1152, 1068 cm^{-1}; UV ($CHCl_3$) λ_{max} 246 nm (ε 450); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (m, 1H, H-1), 3.36 (br t, 1H, J = 3.0 Hz, H-3), 5.48 (dd, 1H, J = 6.0, 10.5 Hz, H-7), 3.16 (d, 1H, J = 10.5 Hz, H-13), 4.54 (d, 1H, J = 10.8 Hz, H-14), 1.27 (s, 3H, Me-18), 1.61 (s, 3H, Me-19), 0.93 (d, 3H, J = 6.6 Hz, Me-20), 3.61 (s, 3H, $-CO_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.2 (d, C-1), 30.5 (t, C-2), 72.4 (d, C-3), 77.4 (s, C-4), 31.4 (t, C-5), 23.2 (t, C-6), 126.4 (d, C-7), 131.8 (s, C-8), 36.6 (t, C-9), 20.7 (t, C-10), 28.9 (t, C-11), 30.0 (d, C-12), 74.8 (d, C-13), 68.9 (d, C-14), 23.9 (s, C-15), 174.4 (s, C-16), 18.1 (t, C-17), 21.0 (q, C-18), 13.8 (q, C-19), 15.3 (q, C-20), 15.4 (t, C-21), 51.4 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{36}O_5$ 380.2563, found 380.2567, 380 (93), 363 (51), 362 (48), 344 (17), 207 (34), 196 (61), 95 (66) 55 (100).

Photolysis of Pyrazoline 25. Compound **25** (22 mg, 0.05 mmol) was dissolved in 5 mL of a mixture of 10% ethyl acetate in hexane, and the resulting solution was irradiated with stirring for 1 h at 25 °C. After concentration, the oil was chromatographed on silica gel (1 g, 20% ethyl acetate in hexane) to provide 20 mg (100%) of **34**. When a solution of **25** (35 mg, 0.086 mmol) in 10% ethyl acetate in hexane was irradiated at 25 °C for 13 h using a 7-59 Corning filter, compound **34** (88%) and a 1:1 mixture of **35** and **36** were obtained. The mixture was flash chromatographed on a short silica gel (3.0 g) column and eluted with 25% ethyl acetate in hexane to furnish 2 mg (6%) of **35** and 2 mg (6%) of **36**.

Data for 34: colorless oil; $[\alpha]^{25}_D$ −33.1° (*c* 4.2, $CHCl_3$); IR (neat) 3446, 1716, 1252, 1195, 1151, 1076 cm^{-1}; UV ($CHCl_3$) λ_{max} 244 nm (ε 400); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (m, 1H, H-1), 3.77 (m, 1H, H-3), 5.19 (br t, 1H, J = 5.1 Hz, H-7), 3.01 (br t, 1H, J = 9.1 Hz, H-13), 3.80 (m, 1H, H-14), 1.11 (s, 3H, Me-18), 1.52 (s, 3H, Me-19), 0.99 (d, 3H, J = 6.6 Hz, Me-20), 3.64 (s, 3H, $-CO_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.9 (d, C-1), 30.5 (t, C-2), 80.6 (d, C-3), 73.8 (s, C-4), 42.9 (t, C-5), 22.0 (t, C-6), 128.6 (d, C-7), 131.6 (s, C-8), 39.7 (t, C-9), 22.4 (t, C-10), 30.3 (t, C-11), 37.4 (d, C-12), 74.5 (d, C-13), 80.6 (d, C-14), 22.1 (s, C-15), 175.3 (s, C-16), 15.0 (t, C-17), 21.7 (q, C-18), 15.6 (q, C-19), 16.9 (q, C-20), 13.2 (t, C-21), 51.7 (q, C-22); HREI-MS m/z [M − H_2O]$^+$ calcd for $C_{22}H_{34}O_4$ 362.2457, found 362.2469, 362 (6), 344 (14), 167 (31), 149 (90), 93 (53), 83 (100).

Data for 35: colorless oil; $[\alpha]^{31}_D$ +9.0° (*c* 0.7, $CHCl_3$); IR (neat) 3439, 1710, 1637, 1273, 1195, 1137 cm^{-1}; UV (MeOH) λ_{max} 220 nm (ε 35000); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.39 (ddd, 1H, J = 6.9, 9.9, 11.7 Hz, H-1), 4.01 (t, 1H, J = 8.0 Hz, H-3), 5.21 (br t, 1H, J = 5.1 Hz, H-7), 2.83 (dd, 1H, J = 1.2, 9.6 Hz, H-13), 4.13 (dd, 1H, J = 1.2, 9.9 Hz, H-14), 6.93 (q, 1H, J = 7.2 Hz, H-17), 1.16 (s, 3H, Me-18), 1.53 (s, 3H, Me-19), 0.98 (d, 3H, J = 6.6 Hz, Me-20), 1.88 (d, 3H, J = 7.2 Hz, Me-21), 3.74 (s, 3H, $-CO_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.5 (d, C-1), 31.6 (t, C-2), 82.3 (d, C-3), 73.8 (s, C-4), 43.3 (t, C-5), 22.4 (t, C-6), 128.7 (d, C-7), 131.6 (s, C-8), 39.8 (t, C-9), 22.3 (t, C-10), 30.5 (t, C-11), 37.7 (d, C-12), 74.0 (d, C-13), 80.8 (d, C-14), 131.4 (s, C-15), 167.4 (s, C-16), 140.8 (d, C-17), 21.4 (q, C-18), 15.6 (q, C-19), 16.9 (q, C-20), 14.3 (q, C-21), 51.5 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{36}O_5$ 380.2563, found 380.2568, 380 (2), 378 (4), 376 (4), 362 (10), 169 (46), 83 (79), 55 (100).

Data for 36: colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.09 (q, 1H, J = 7.2 Hz, H-17), 1.92 (d, 3H, J = 7.2 Hz, Me-21), 3.64 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.9 (d, C-3), 73.6 (s, C-4), 73.8 (d, C-13), 81.1 (d, C-14), 136.2 (s, C-15), 148.1 (d, C-17), 14.1 (q, C-21), 51.4 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{36}O_5$ 380.2563, found 380.2592, 380 (3).

Thermolysis of Pyrazoline 25. A solution of pyrazoline **25** (15 mg, 0.035 mmol) in benzene (10 mL) was treated with glacial acetic acid (3 drops), warmed to 90−100 °C for 5 days, cooled, and concentrated to leave a crude residue (20 mg) that was purified by means of silica gel chromatography (1 g, elution with 20% ethyl acetate in hexane) to give 10 mg (75%) of a 3:1 mixture of compounds **34** and **36**, respectively.

Treatment of 4,14-Eupalmeroic acid (18) with Diazomethane and Thermolysis of the Mixture of Pyrazolines 23 and 24. A solution of diazomethane in ether (25 mL) was added to a solution of **18** (271 mg, 0.77 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 30 min prior to being concentrated and stored under high vacuum. The resulting oil (238 mg, 76%), which consisted of a 1:1 mixture of pyrazolines, was used in the next step without further purification. A solution of **23** and **24** (73 mg, 0.18 mmol) in toluene (4 mL) was treated with glacial acetic acid (1 mL), warmed to 115 °C for 4.5 h, cooled, and concentrated to leave an oil that was purified by means of silica gel chromatography (2.4 g, elution with chloroform), giving 15 mg (22%) of derivative **32**, 13 mg (18%) of **38**, and ca. 1−2 mg (2%) of **39**.

Data for 38: colorless oil; $[\alpha]^{25}_D$ +21.9° (*c* 2.1, $CHCl_3$); IR (neat) 3396, 1715, 1231, 1148, 1068, 1036 cm^{-1}; UV (MeOH) λ_{max} 225 nm (ε 3100); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.90 (m, 1H, H-1), 3.33 (br t, 1H, J = 2.9 Hz, H-3), 5.47 (m, 1H, H-7), 2.88 (d, 1H, J = 10.6 Hz, H-13), 4.06 (d, 1H, J = 11.0 Hz, H-14), 6.05 (q, 1H, J = 7.1 Hz, H-17), 1.29 (s, 3H, Me-18), 1.59 (s, 3H, Me-19), 0.91 (d, 3H, J = 6.5 Hz, Me-20), 1.86 (d, 3H, J = 7.1 Hz, Me-21), 3.74 (s, 3H, $-CO_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.4 (d, C-1), 32.5 (t, C-2), 71.6 (d, C-3), 77.7 (s, C-4), 31.1 (t, C-5), 23.1 (t, C-6), 126.2 (d, C-7), 131.9 (s, C-8), 36.5 (t, C-9), 20.6 (t, C-10), 28.8 (t, C-11), 30.0 (d, C-12), 75.0 (d, C-13), 68.9 (d, C-14), 133.5 (s, C-15), 168.6 (s, C-16), 137.5 (d, C-17), 21.0 (q, C-18), 13.7 (q, C-19), 15.2 (q, C-20), 15.8 (q, C-21), 51.2 (q, C-22); HREI-MS m/z [M]$^+$ calcd for $C_{22}H_{36}O_5$ 380.2563, found 380.2572, 380 (100), 362 (34), 349 (17), 196 (40), 180 (18), 152 (41).

Data for 39: colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (q, 1H, J = 7.2 Hz, H-17), 1.87 (d, 3H, J = 7.2 Hz, Me-21), 3.71 (s, 3H, $-CO_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.7 (d, C-3), 75.6 (d, C-13), 67.9 (d, C-14).

Dehydration of 3,14-Eupalmeroic Acid (17) with *p*-Toluenesulfonic Acid Hydrate. To a solution of **17** (99 mg, 0.28 mmol) in dry benzene (15 mL) was added PTSA·H_2O (a few crystals). The solution was heated to 75 °C for 2 h and then cooled, quenched with saturated $NaHCO_3$, and extracted with benzene (3 × 30 mL). The combined organic layers were washed with brine and concentrated, and the residue was purified by normal-phase HPLC (Partisil-10, 15% 2-propanol in hexane) to give 56 mg (60%) of **40** and 19 mg (20%) of **41**. An attempt to prepare δ-lactone **42** by dehydration of 4,14-eupalmeroic acid (**18**) under similar reaction conditions furnished unchanged starting material.

Data for 40: colorless oil; $[\alpha]^{25}_D$ −1.5° (*c* 3.4, $CHCl_3$); IR (neat) 3568 (sharp), 1709, 1641, 1272, 1234, 1155, 1135, 1093 cm^{-1}; UV (CH_3OH) λ_{max} 212 nm (ε 9900); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.86 (m, 1H, H-1), 4.15 (dd, 1H, J = 4.1, 9.4 Hz, H-3), 1.88 (m, 1H, H-7), 2.33 (m, 1H, H-7′), 5.14 (br t, 1H, J = 8.3 Hz, H-9), 4.43 (dd, 1H, J = 5.7, 9.5 Hz, H-13), 3.91 (dd, 1H, J = 5.5, 12.0 Hz, H-14), 5.44 (d, 1H, J = 2.6 Hz, H-17), 6.37 (d, 1H, J = 2.8 Hz, H-17′), 1.11 (s, 3H, Me-18), 1.55 (s, 3H, Me-19), 1.10 (d, 3H, J = 6.2 Hz, Me-20); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.3 (d, C-1), 29.0 (t, C-2), 88.8 (d, C-3), 74.2 (s, C-4), 27.4 (t, C-5), 17.7 (t, C-6), 38.7 (t, C-7), 134.4 (s, C-8), 126.9 (d, C-9), 23.6 (t, C-10), 35.9 (t, C-11), 30.4 (d, C-12), 83.7 (d, C-13), 78.8 (d, C-14), 136.7 (s, C-15), 163.8 (s, C-16), 125.1 (t, C-17), 22.6 (q, C-18), 15.1 (q, C-19), 15.2 (q, C-20); HREI-MS m/z [M]$^+$

calcd for $C_{20}H_{30}O_4$ 334.2144, found 334.2176, 334 (3), 316 (73), 277 (11), 164 (28), 121 (62), 93 (57), 81 (100).

Data for 41: colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.96 (m, 1H, H-1), 4.19 (dd, 1H, J = 3.5, 9.9 Hz, H-3), 5.28 (dd, 1H, J = 5.4, 11.3 Hz, H-9), 4.41 (dd, 1H, J = 4.8, 11.1 Hz, H-13), 3.97 (dd, 1H, J = 4.9, 12.3 Hz, H-14), 5.48 (d, 1H, J = 2.3 Hz, H-17), 6.42 (d, 1H, J = 2.8 Hz, H-17′), 1.10 (s, 3H, Me-18), 1.69 (s, 3H, Me-19), 1.16 (d, 3H, J = 6.5 Hz, Me-20); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.7 (d, C-1), 29.9 (t, C-2), 89.1 (d, C-3), 74.3 (s, C-4), 32.6 (t, C-5), 19.2 (t, C-6), 31.4 (t, C-7), 135.1 (s, C-8), 125.6 (d, C-9), 27.2 (t, C-10), 32.9 (t, C-11), 36.3 (d, C-12), 83.0 (d, C-13), 79.9 (d, C-14), 137.0 (s, C-15), 163.8 (s, C-16), 125.8 (t, C-17), 21.9 (q, C-18), 23.7 (q, C-19), 17.1 (q, C-20); HREI-MS m/z $[M - H_2O]^+$ calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2056, 316 (25), 277 (16), 111 (48), 97 (46), 81 (60), 57 (100).

Trifluoroacetylation of 4,14-Eupalmeroic Acid (18). Trifluoroacetic anhydride (0.6 mL, 4.46 mmol) was added to a solution of **18** (26 mg, 0.075 mmol) in benzene-d_6 (1 mL). After 22 h at 25 °C, the mixture was concentrated. Purification of the residue by chromatography on silica gel (elution with a 95:5:0.5 mixture of chloroform/MeOH/acetic acid) provided ditrifluoroacetate **43** as a colorless oil (18 mg, 44%).

Data for 43: colorless oil; $[\alpha]^{30}_D$ −12.8° (c 3.7, MeOH); IR (neat) 3600−3100 (broad), 1710 (broad), 1621, 1204, 1139, 1069 cm^{-1}; UV (MeOH) λ_{max} 210 nm (ϵ 5000); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.76 (m, 1H, H-1), 4.83 (br t, 1H, J = 2.6 Hz, H-3), 5.53 (br t, 1H, J = 9.5 Hz, H-7), 4.57 (d, 1H, J = 11.0 Hz, H-13), 4.44 (br d, 1H, J = 11.0 Hz, H-14), 5.68 (br s, 1H, H-17), 6.48 (br s, 1H, H-17′), 1.30 (s, 3H, Me-18), 1.60 (s, 3H, Me-19), 0.78 (d, 3H, J = 6.6 Hz, Me-20), 3.30 (br s, exchangeable, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.6 (d, C-1), 30.1 (t, C-2), 77.2 (d, C-3), 76.0 (s, C-4), 29.7 (t, C-5), 22.7 (t, C-6), 125.8 (d, C-7), 132.1 (s, C-8), 36.4 (t, C-9), 20.3 (t, C-10), 28.8 (t, C-11), 27.8 (d, C-12), 81.0 (d, C-13), 68.3 (d, C-14), 138.6 (s, C-15), 170.0 (s, C-16), 131.5 (t, C-17), 20.6 (q, C-18), 13.7 (q, C-19), 13.9 (q, C-20), 157.8 (q, C-21), 114.7 (q, C-22), 157.0 (q, C-23), 114.5 (q, C-24). The resonance lines due to C-1 and C-15 were broad signals of very low intensity. Unfortunately, this compound decomposed before the HREI mass spectrum could be recorded.

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Supporting Information Available: Proposed mechanism for the formation of diepoxide **5** and copies of the ^{1}H and ^{13}C NMR spectra for analogues **4**−**6**, **8**−**10**, **12**, **13**, **15**−**18**, **20**, **21**, **23**-**25**, **27**, **28**, **30**, **32**, **34**, **35**, **38**, and **40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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