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ANTICANCER SESQUITERPENE LACTONES OF *MICHELIA COMPRESSA* (MAGNOLIACEAE)*

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Key Word Index—*Michelia compressa*; Magnoliaceae; sesquiterpene lactones; anticancer activity; partial synthesis.

Abstract—Investigation of the cytotoxic active components of *Michelia compressa* afforded two new cytotoxic sesquiterpene lactones, michelenolide and micheliolide. Parthenolide, costunolide, santamarine, reynosin and liriodenine were also isolated and exhibited cytotoxic activity. The known sesquiterpene lactones, lanuginolide and dihydroparthenolide, were isolated but were not active. Two other new inactive sesquiterpene lactones, compressanolide and dihydroreynosin, were also obtained. The structures of michelenolide and micheliolide were confirmed by partial synthesis from parthenolide and the structure of compressanolide by partial synthesis from dihydroparthenolide.

In a continuing search for new anticancer agents from higher plants, an aqueous alcoholic extract of the stem bark of *Michelia compressa* (Maxim.) Sarg. (Magnoliaceae) was found to be active against the 9KB carcinoma of the nasopharynx in cell culture [1]. *Michelia* species have been used by indigenous peoples in the treatment of cancer. For example, *Michelia champaca* has been used in India for the treatment of abdominal tumors and *M. hypoleuca* and *M. officinalis* for carcinomatous sores and leukemia respectively, in China [2]. Experimentally, *M. grandiflora*, *M. compressa* and *M. kobus* have demonstrated anticancer activity in various tumor systems [3].

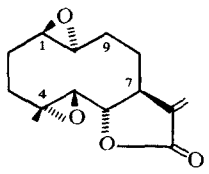
Fractionation of the methanol extract of the root bark of *Michelia compressa* and evaluation of the fractions indicated that the cytotoxic activity was located in the chloroform soluble fraction. Chromatography of this fraction afforded michelenolide (**1**), micheliolide (**2**), compressanolide (**3**)† and dihydroreynosin (**4**) which are new sesquiterpene lactones; parthenolide (**5**), dihydroparthenolide (**6**), costunolide (**7**), lanuginolide (**8**), reynosin (**9**) and santamarine (**10**), as known sesquiterpene lactones; and liriodenine (**11**), a known alkaloid. This paper is concerned with the cytotoxicity and structure elucidation of the new sesquiterpene lactones **1**–**4**.

Michelenolide (**1**) crystallized from ether as colorless needles, mp 160°. The mass spectrum indicated a molecular ion at *m/e* 264 in agreement with a molecular formula $C_{15}H_{20}O_4$. The NMR spectrum established michelenolide as a sesquiterpene lactone [4]. The typical exomethylene protons of an α,β-unsaturated-γ-lactone were observed at 5.63 (*d*, J = 2.5 Hz) and 6.34 ppm (*d*, J = 2.5 Hz), and this functionality was confirmed by the observation of a carbonyl absorption at 1755 cm^{-1} in the IR spectrum. Two three-proton singlets were observed at 1.35 and 1.41 ppm, which could be attributed to methyl groups attached to carbon bearing oxygen. Two methine signals at 2.86 (*dd*, J = 9.0, 2.0 Hz) and 2.91 ppm (*d*, J = 9.0 Hz) were assigned to protons on carbon bearing oxygen. No protons were exchanged on addition of D_2O. Evaluation of these data and consideration of the molecular formula suggested that michelenolide had two trisubstituted epoxide groups. Biogenetic considerations indicated that michelenolide was a germacrenolide sesquiterpene lactone [5] having two epoxide group C_1–C_{10} and C_4–C_5. The stereochemistries of the six chiral centers of michelenolide were determined by chemical interconversion and analysis of the coupling constants. The C_6 proton was assigned to the triplet at 3.95 ppm (J = 9.0 Hz), there by describing the stereochemistry of the C_6 and C_7 protons as *trans*. The doublet at 2.91 ppm was assigned to the C_5 proton and the doublet of doublets at 2.86 ppm to the C_1 methine proton.

The stereochemistry of costunolide (**7**), determined by X-ray analysis [5, 6], is characterized by two *trans* olefinic functionalities in which the methyl groups are oriented on the same side of the germacrenolide ring, and are pseudoaxial. Treatment of costunolide (**7**) with 1.2 equivalents of *m*-chloroperbenzoic acid gave an epoxide in which the C_1–C_{10} olefinic bond had been attacked both regioselectively and stereoselectively. The PMR spectrum of this compound showed a doublet of doublets (J = 10.0, 2.0 Hz) for the C_1-proton at 2.73 ppm and a singlet for the epoxide methyl group at 1.16 ppm. The coupling constants of the C-1 proton indicate an α-orientation of the C-1 proton, and that costunolide monoepoxide has the structure **12**.

* Part 7 in a series 'Potential Anticancer Agents', for Part 6 see: Koike, K., Bevelle, C., Cordell, G. A. and Farnsworth, N. R. (1978) *Chem. Pharm. Bull.* in press.

† In a preliminary communication, *Lloydia* **39**, 469 (1976), this compound was refered to as formosanolide. A revision of species name required a revision in the name of the compound to compressanolide.



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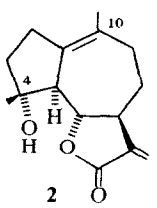

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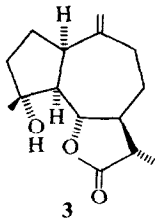

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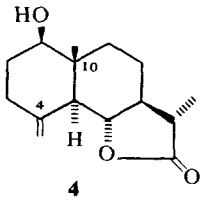

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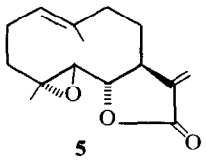

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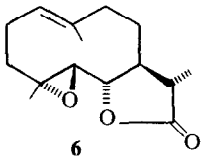

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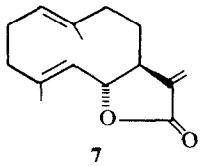

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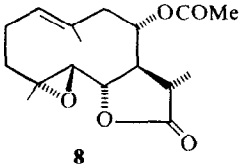

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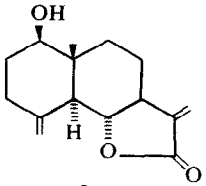

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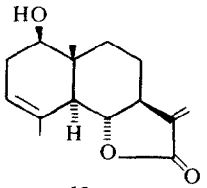

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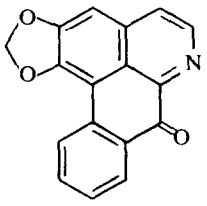

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The close structural relationship of michelenolide to parthenolide (**5**) suggested a possible conversion of **5** to michelenolide by epoxidation of the C_1–C_{10} double bond. Treatment of **5** with *m*-chloroperbenzoic acid gave a monoepoxide of parthenolide identical to michelenolide by comparison of their PMR and mass spectra, mmr and chromatographic properties. The stereochemistry of parthenolide at C_1, C_6, C_7 and C_{10} has been established [7], and the stereochemistry of the C_4–C_5 epoxide has been suggested [8]. An X-ray analysis [9] has recently confirmed these stereochemical assignments. As with costunolide (**7**) the epoxidation of parthenolide (**5**) suggested, on the basis of the C_1 coupling constants, that the stereochemistry of the C_1–C_{10} epoxide was *trans*, that the C_1 proton was α and the C-10 methyl group β. The structure and stereochemistry of michelenolide are therefore represented by **1**.

Micheliolide (**2**) crystallized from ether as colorless needles, mp 141°. From the mass spectrum, the MW of micheliolide was found to be 248, in agreement with a molecular formula $C_{15}H_{20}O_3$. The NMR spectrum revealed the exo-methylene protons, characteristic of an α,β-unsaturated-γ-lactone, as doublets (J = 3 Hz) at 5.50 and 6.20 ppm. Two signals attributable to methyl groups were observed. One, a singlet at 1.31 ppm could be assigned to a methyl group attached to a carbon further substituted by an oxygen function. A broadened doublet was observed at 1.69 ppm and assigned to a vinyl methyl group. No olefinic protons were observed for this double bond which must therefore be tetrasubstituted. The second oxygen function other than the α-methylene lactone, was proved to be a hydroxyl group, a singlet at 2.57 ppm disappearing on the addition of D_2O.

Consideration of the PMR data and molecular formula indicated that micheliolide had the guaiane skeleton. Placement of the double bond and of the tertiary hydroxy group were facilitated by the observation of a triplet for the methine proton at C-6, indicating proximity of two protons. Consequently, the double bond can be placed at the C_1–C_{10} position and the hydroxyl group at C-4. Micheliolide therefore has the gross structure **13** in which it remains to determine the stereochemistry at positions 4, 5, 6 and 7. The relative stereochemistry of C-5, 6 and 7 was deduced from the coupling constants of the C-6 proton. The large observed coupling constant (J = 10 Hz) for this proton with each of the adjacent protons is characteristic of a guaianolide having the 5, 6, and 7 protons α, β and α respectively [4].

The configuration at C-4 was determined by partial synthesis. Treatment of parthenolide (**5**) with dry HCl gas in anhydrous ether at 0° gave a product resulting from transannular cyclization [7]. Purification by preparative TLC afforded a guaianolide sesquiterpene lactone identical to micheliolide by comparison of the PMR and IR spectra, and mixture melting points. The absolute stereochemistry of parthenolide (**5**) is known from the recent X-ray analysis [9] and the reaction mechanism for the conversion of **5** to **2** leaves the stereochemistry at C-4 intact. The hydroxyl group at C-4 in micheliolide therefore has the α-configuration, and the complete stereochemistry of micheliolide is represented by **2**.

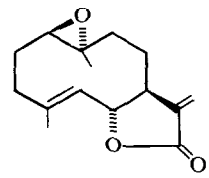
Compressanolide (**3**) was obtained as a pale yellow oil. The mass spectrum indicated a molecular ion at *m/e* 250 in agreement with the molecular formula $C_{15}H_{22}O_3$. The IR spectrum showed the presence of a saturated γ-lactone (1770 cm^{-1}) and an exo-methylene group (1630 and 892 cm^{-1}). In the NMR spectrum, one doublet methyl signal (J = 6.7 Hz) was observed at 1.22 ppm and a singlet methyl at 1.29 ppm. The latter could be assigned to a methyl group attached to a carbon further substituted by oxygen. One hydroxyl proton was found at 2.63 ppm, which was exchanged on addition of D_2O. The absence of a methine signal in the region of 3.2 ppm suggested that a methyl tertiary alcohol was present. A double doublet methine proton at 4.04 ppm (J = 8.5 and 10.7 Hz) and a singlet two proton exo-methylene signal at 4.95 ppm completed the main features of the PMR spectrum.

Oxidation of compressanolide by periodate–per-

manganate reagent [10, 11] gave a keto compound, the IR spectrum of which showed a seven-membered ketone at 1705 cm^{-1}. Thus the exo-methylene could be placed on a seven-membered ring. Evaluation of the above data and biogenetic considerations indicated that compressanolide should be a guaiane sesquiterpene lactone [5] having an exo-methylene on the seven-membered ring and a methyl tertiary alcohol. Although the structure **14** was considered likely for compressanolide, it remained to confirm this structure assignment and determine the stereochemistry. This was achieved by partial synthesis from dihydroparthenolide (**6**) having the stereochemistry shown.

Treatment of dihydroparthenolide (**6**) with dry gas in anhydrous ether at 0° for 5 min gave a mixture of products resulting from the transannular cyclization [9] of the epoxygermacrenolide system. Purification by preparative TLC afforded a major guaianolide sesquiterpene lactone identified as dihydromicheliolide (**15**). The compound was identical (NMR, IR, mmp) with an authentic sample prepared by the $NaBH_4$ reduction of micheliolide (**2**). The minor product of the acid-catalyzed cyclization was also a guaianolide sesquiterpene, identical to compressanolide by comparison of the NMR spectrum and chromatographic properties. The stereochemistry of dihydroparthenolide (**6**) is defined at the reacting centres C-1, C-4, C-5 and C-10, and assuming a concerted transannular cyclization, compressanolide therefore has the complete structure **3**.

Dihydroreynosin (**4**), mp 129°, crystallized as colorless needles from hexane. The mass spectrum of dihydroreynosin indicated a molecular ion *m/e* 250 in agreement with a molecular formula of $C_{15}H_{22}O_3$. The NMR spectrum of dihydroreynosin was very similar to that of reynosin (**9**) showing similar chemical shifts and complexity for the C-1 proton, the C-4 exo-methylene, the C-5 and C-6 protons and the C-10 methyl group [4]. The only major differences were an absence of the C-13 exo-methylene protons and the presence of a three-proton doublet ($J = 6$ Hz) at 1.21 ppm. The new doublet could be attributed to a methyl group produced by



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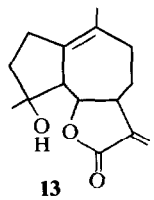

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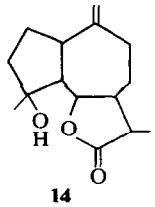

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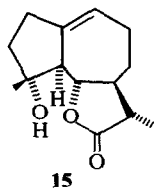

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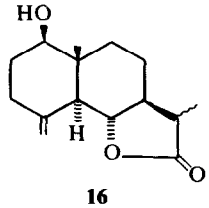

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Table 1. Cytotoxic activities of the isolates of *M. compressa*

Compound		NSC	9KB (μg/ml)*
Michelenolide	(**1**)	270915	1.0
Micheliolide	(**2**)	280451	2.5
Compressanolide	(**3**)		inactive
Dihydroreynosin	(**4**)		inactive
Parthenolide	(**5**)	157035	0.45
Dihydroparthenolide	(**6**)		inactive
Costunolide	(**7**)	106404	0.69
Lanuginolide	(**8**)		inactive
Reynosin	(**9**)	155623	inactive
Santamarine	(**10**)	138267	1.1
Liriodenine	(**11**)	93681	3.8

* A compound is active if it exhibits $ED_{50} \leqslant 4$ μg/ml.

reduction of the 11,13-exo-methylene on the γ-lactone ring. Dihydroreynosin therefore has the gross structure **16**. The stereochemistry of the C-11 methyl group was determined by the method of Narayanan *et al.* [12].

These workers described how the configuration of a C_{11}-Me group can be assigned by measurement of the shift of the methyl protons on changing the solvent from chloroform to benzene. An upfield shift of between 0.23 and 0.29 ppm is indicaive of an α-methyl group, a more substantial shift being indicative of a β-configuration. The NMR spectrum of dihydroreynosin in C_6D_6 showed a doublet for the C_{11}-methyl group at 1.01 ppm, corresponding to an upfield shift of 0.21 compared to the spectrum in $CDCl_3$. The C_{11}-methyl group therefore has the α-configuration and dihydroreynosin has the structure **4**.

The application of the benzene-induced chemical shift was also attempted with the guaianolide, compressanolide (**3**). The NMR spectrum of compressanolide in C_6D_6 showed a doublet for the C_{11}-methyl group centered at 0.95 ppm. This represents an upfield shift of the methyl protons by 0.27 ppm on changing the solvent from $CDCl_3$ to C_6D_6; the C_{11}-methyl group therefore has the α-configuration. This point has already been proven from the corresponding site in dihydroreynosin (**4**).

In addition to the new sesquiterpene lactones discussed above, six known sequiterpene lactones and an alkaloid were isolated. The sesquiterpene lactones obtained were parthenolide (**5**), dihydroparthenolide (**6**), costunolide (**7**), lanuginolide (**8**), reynosin (**9**), and santamarine (**10**). The alkaloid isolated was liriodenine (**11**). Each of the known compounds was identified with an authentic sample by comparison of physical data and/or mmp determination. Liriodenine (**11**) has been reported isolated from the heartwood of *M. compressa* var. *formosana* [13].

The biological activities of the constituents of *Michelia compressa* are listed in Table 1. All of the compounds having an α,β-unsaturated γ-lactone moiety (except **9**) were active in the Eagle's carcinoma of the nasopharynx cell culture system. The cytotoxicity of costunolide (**7**) [14] and liriodenine (**11**) [15] have been reported previously.

EXPERIMENTAL

Plant material. The root bark of *Michelia compressa* (Maxim.) Sarg. (Magnoliaceae) was collected in Taiwan in 1974. Identification was made by Dr R. E. Perdue, Jr.

Extraction and isolation. Root bark material (20 kg) of *Michelia compressa* (Magnoliaceae) was extracted with MeOH and the extract evapd *in vacuo*. H_2O (5 l.) was added to the residue and the mixture extracted with $CHCl_3$ (2l. × 3). The $CHCl_3$ soluble fraction, after drying and evapn, weighed 470 g and exhibited activity in both the P-388 *in vivo* and 9KB test systems. The aq phase was inactive. The $CHCl_3$ soluble fraction (120 g) was chromatographed on Si gel (Merck PF-254), eluting with $CHCl_3$. Repeated chromatography of the crude column cuts successively afforded costunolide (**7**), parthenolide (**5**), dihydroparthenolide (**6**), micheliolide (**2**), lanuginolide (**8**), compressanolide (**3**), santamarine (**10**), dihydroreynosin (**4**), reynosin (**9**), michelenolide (**1**) and liriodenine (**11**).

Michelenolide (**1**). Crystallization from ether gave colorless needles: mp 160–162°, IR ν_{max}^{KBr} cm^{-1} 1757 and 1660 (α,β-unsaturated γ-lactone), and 890 (exomethylene). MS: *m/e* 264 (M^+, 1.0%). NMR ($CDCl_3$): δ. 1.35 (*s*, 3H, C_4-Me or C_{10}-Me), 1.41 (*s*, 3H, C_{10}-Me or C_4-Me), 2.86 (*dd*, 1H *J* = 9 and 2 Hz, C_1-H), 2.91 (*d*, 1H, *J* = 9 Hz, C_5-H), 3.95 (*t*, 1H, *J* = 9 Hz, C_6-H), 5.63 (*d*, 1H, *J* = 2.5 Hz, C_{13}-H_a), and 6.34 ppm (*d*, 1H, *J* = 2.5 Hz, C_{13}-H_b). Mass measurement, Obsd: 264.1362: Calcd. for $C_{15}H_{20}O_4$, 264.1362.

Micheliolide (**2**). Crystallization from ether gave colorless needles: mp 141°, MS: *m/e* 248 (M^+, 22.2%), 230 (M^+-H_2O, 39.2), 190 (85.9) and 43 (100). NMR ($CDCl_3$): δ 1.31 (*s*, 3H, C_4-Me), 1.69 (*br d*, 3H, *J* = 1, 6 Hz, C_{10}-Me), 3.82 (*t*, 1H, *J* = 10 Hz, C_6-H), 5.50 (*d*, 1H, *J* = 3 Hz, C_{13}-H_a) and 6.20 ppm (*d*, 1H, *J* = 3 Hz, C_{13}-H_b). Mass measurement, Obsd: 248.14302; Calcd. for $C_{15}H_{20}O_3$, 248.14125.

Compressanolide (**3**). The material was obtained as a yellow oil: IR ν_{max}^{film} cm^{-1}: 1770 (γ-lactone), and 1639 and 892 (exomethylene). MS: *m/e* 250 (M^+, 26.1%), 232 (M^+-H_2O, 75.4) and 43 (100). NMR ($CDCl_3$): δ 1.22 (*d*, 3H, *J* = 6.7 Hz, C_{11}-Me), 1.29 (*s*, 3H, C_4-Me), 2.63 (*s*, 1H, readily removed with D_2O, OH), 4.04 (*dd*, 1H, *J* = 8.5 and 10.7 Hz, C_6-H), and 4.95 ppm (*br s*, 2H, C_{10}=CH_2). Mass measurement, Obsd: 250.1568; Calcd. for $C_{15}H_{22}O_3$, 250.1568.

Dihydroreynosin (**4**). Crystallization from hexane gave a colorless powder: mp 129°, IR ν_{max}^{KBr} cm^{-1}: 3460 (OH), 1752 (γ-lactone) and 893 (exo-methylene). MS: *m/e* 250 (M^+-H_2O, 100). NMR ($CDCl_3$): δ 0.81 (*s*, 3H, C_{10}-Me), 1.21 (*d*, 3H, *J* = 6,5 Hz, C_{11}-Me), 1.66 (*s*, 1H readily removed with D_2O, OH), 3.48 (*dd*, 1H, *J* = 4.5 and 10.5 Hz, C_1-H), 4.03 (*t*, 1H *J* = 10 Hz, C_6-H), 4.82 (*br s*, 1H, C_4=CH_2) and 4.97 ppm (*br s*, 1H, C_4=CH_2). Mass measurement, Obsd: 250.1577; Calcd. for $C_{15}H_{22}O_3$, 250.1568.

Parthenolide (**5**). Crystallization from ether–hexane gave a colorless powder: mp 110°; NMR ($CDCl_3$): δ 1.30 (*s*, 3H C_4-Me), 1.72 (*br s*, 3H, C_{10}-Me), 2.78 (*d*, 1H, *J* = 8.5 Hz, C_5-H), 3.91 (*t*, 1H *J* = 8.5 Hz, C_6-H), 5.27 (*br*, 1H, C_1-H), 5.62 (*d*, 1H, *J* = 3 Hz, C_{13}-H_a) and 6.31 ppm (*d*, 1H, *J* = 3 Hz, C_{13}-H_b). This compound was identical with an authentic sample (NMR and mmp)

Dihydroparthenolide (**6**). Crystallization from ether–hexane gave a colorless powder: mp 127 , IR ν_{max}^{KBr} cm^{-1}: 1770 (γ-lactone). NMR ($CDCl_3$): δ 1.26 (*s*, 3H, C_4-Me), 1.25 (*d*, 3H, *J* = 6 Hz, C_{11}-Me), 1.67 (*br s*, 3H, C_{10}-Me), 2.67 (*d*, 1H *J* = 9 Hz, C_6-H) and 5.18 ppm (*m*, 1H, C_1-H). This compound was identical with an authentic sample (NMR and mmp).

Costunolide (**7**). Crystallization from ether gave colorless needles: mp 106°, IR ν_{max}^{KBr} cm^{-1}: 1765 and 1665 (α,β-unsaturated γ-lactone). NMR ($CDCl_3$): δ 1.43 (*d*, 3H, *J* = 1 Hz, C_{10}-Me or C_4-Me), 1.69 (*d*, 3H, *J* = 1 Hz, C_4-Me or C_{10}-Me), 4.54 (*t*, 1H, *J* = 10 Hz, C_6-H), 4.5–5.0 (*br*, 1H, C_1-H), 4.79 (*m*, 1H, C_5-H), 5.52 (*d*, 1H, *J* = 3 Hz, C_{13}-H_a) and 6.24 ppm (*d*, 1H, *J* = 3 Hz, C_{13}-H). This compound was identical with an authentic sample (NMR and mmp).

Lanuginolide (**8**). Crystallization from ether gave colorless needles: mp 175°, MS: *m/e* 308 (M^+, 4.5%), 248 (M^+-Me-COOH, 51.3 and 43 (100). NMR ($CDCl_3$): δ 1.28 (*s*, 3H, C_4-Me), 1.42 (*d*, 3H, *J* = 6 Hz, C_{11}-Me), 1.81 (*br s*, 3H, C_{10}-Me), 2.65 (*d*, 1H *J* = 9 Hz, C_5-H), 3.99 (*t*, 1H *J* = 9 Hz, C_5-H) 4.91 (*dd*, 1H *J* = 12.3 and 6.7 Hz, C_8-H) and 5.30 ppm (*m*, 1H, C_1-H). This compound was identical with an authentic sample NMR and mmp).

Reynosin (**9**). Crystallization from ether–hexane gave a colorless powder: mp 143°, MS: *m/e* 248 (M^+, 10.5%) and 230 (M^+-H_2O, 100). NMR ($CDCl_3$): δ 0.80 (*s*, 3H, C_{10}-Me), 3.56 (*dd*, 1H, *J* = 5 and 10.6 Hz, C_1-H), 4.03 (*t*, 1H, *J* = 11 Hz, C_6-H), 4.82 (*br s*, 1H, C_4=CH_2), 4.96 (*br s*, 1H, C_4=CH_2), 5.42 (*d*, 1H, *J* = 3 Hz, C_{13}-H_a) and 6.06 ppm (*d*, 1H, *J* = 3 Hz, C_{13}-H_b). This compound was identical with an authentic sample (NMR, mmp).

Santamarine (**10**). Crystallization from hexane gave a colorless powder: mp 130°, MS: *m/e* 248 (M^+, 100%) and 230 (M^+-H_2O, 24.7). NMR ($CDCl_3$): δ 0.87 (*s*, 3H, C_{10}-Me), 1.85 (*br s*, 3H, C_4-Me), 3.68 (*dd*, 1H, *J* = 7 and 10 Hz, C_1-H), 3.96 (*t*, 1H, *J* = 10 Hz, C_6-H), 5.40 (*m*, 1H, C_3-H), 5.42 (*d*, 1H, *J* = 3 Hz, C_{13}-H_a) and 6.09 ppm (*d*, 1H, *J* = 3 Hz, C_{13}-H_b). This compound was identified as santamarine by comparison of the NMR spectrum [5].

Liriodenine (**11**). Crystallization from $CHCl_3$ gave yellow needles: mp 286°, IR ν_{max}^{KBr} cm^{-1}: 1650, 1615 and 1600. MS: *m/e* 275 (M^+, 100%) and 246 (M^+-HCO, 17). UV λ_{max}^{MeOH} nm 248 (31 600), 268 (25 800), 310 (8 900) and 417 (12 100). NMR (DMSO-d_6): δ 6.52 (*s*, 2H, O—CH_2—O), 7.59 (*s*, 1H, C_5-H), 7.7–8.6 (M, 4H, aromatic H), 8.04 (*d*, 1H, *J* = 5.25 Hz, C_3-H) and 8.82 ppm (*d*, 1H, *J* = 5.2 Hz, C_4-H). This compound was identical with an authentic sample (mmp).

Partial synthesis of michelenolide (**1**). Parthenolide (**5**, 30 mg) was treated with 1.1 equivalent of *m*-chloroperoxybenozic acid in $CHCl_3$ at room temp. for 20 min. The reaction mixture was shaken with 5% Na sulfite in H_2O and washed with satd aq. $NaHCO_3$. The $CHCl_3$ phase was dried, filtered and evapd. The crude product was purified on prep-TLC eluting with $CHCl_3$–Et_2O (1:1). The band at R_f 0.24 was removed, eluted with $CHCl_3$, and the residue crystallized from Et_2O to afford **1** (17 mg): mp 160°, MS: *m/e* 264 (M^+, 1.1%) and 43 (100). NMR ($CDCl_3$): δ 1.35 (*s*, 3H, C_4-Me or C_{10}-Me), 1.40 (*s*, 3H, C_{10}-Me or C_4-Me), 2.90 (*d*, 1H, *J* = 8.8 Hz, C_5-H), 3.95 (*t*, 1H *J* = 8.8 Hz, C_6-H), 5.62 (*d*, 1H, *J* = 3.3 Hz, C_{13}-H_a) and 6.34 ppm (*d*, *J* = 3.3 Hz, C_{13}-H_b). This compound was identical to natural michelenolide (**1**) (NMR and mmp).

Epoxidation of costunolide (**7**) *to monoepoxycostunolide* (**12**). Costunolide (**7**, 30 mg) was treated with 1.2 equivalent of *m*-chloroperbenzoic acid in $CHCl_3$ at room temp. for 15 min. The reaction mixture was treated with 5% Na sulfite in H_2O and washed with satd aq. $NaHCO_3$ and H_2O. Working up the $CHCl_3$ soln afforded a residue which was crystallized from ether to afford **12** as colorless needles: mp 117–119°, MS: *m/e* 248 (M^+, 45.5%) and 28 (100). NMR ($CDCl_3$): δ 1.16 (*s*, 3H, C_{10}-Me), 1.86 (*d*, 3H, *J* = 1 Hz, C_4-Me), 2.73 (*dd*, 1H *J* = 10 and 2 Hz, C_1-H), 4.62 (*t*, 1H, *J* = 10 Hz, C_6-H), 5.32 (*br d*, 1H, *J* = 10 Hz, C_5-H), 5.52 (*d*, 1H, *J* = 2.5 Hz, C_{13}-H_a) and 6.27 ppm (*d*, 1H, *J* = 2.5 Hz, C_{13}-H_b).

Acid-catalyzed rearrangement of parthenolide (**5**) *to micheliolide* (**2**). Parthenolide (**5**, 75 mg) was treated with dry HCl gas in ether at 0° for 5 min. The reaction soln was diluted with H_2O, washed with satd aq $NaHCO_3$, and the ether phase dried and evapd. The residue was chromatographed on prep-TLC and the zone at R_f 0.31 removed and eluted with $CHCl_3$. The crude product was crystallized from ether to afford **2** (17 mg): mp 134°, MS: *m/e* 248 (M^+, 22%) and 43 (100). NMR ($CDCl_3$): σ 1.31 (*s*, 3H, C_4-Me), 1.69 (*br s*, 3H, C_{10}-Me), 3.84 (*t*, 1H, *J* = 10 Hz, C_6-H), 5.51 (*d*, 1H *J* = 3 Hz, C_{13}-H_a) and 6.23 ppm (*d*, 1H, *J* = 3 Hz, C_{13}-H_b). This compound was identical to natural micheliolide (**2**) (NMR and mmp).

$NaBH_4$ reduction of micheliolide (**2**) *to dihydromicheliolide* (**15**). A soln of micheliolide (**2**, 10 mg) in MeOH (5 ml) was treated at 0° with $NaBH_4$ and stirred for 1 hr at room temp The mixture was acidified with HOAc, H_2O added and then extracted with $CHCl_3$. The $CHCl_3$ soln was dried and evapd. The crude dihydromicheliolide (**15**) was purified by prep-TLC and crystallized from ether: mp 128°, IR ν_{max}^{KBr} cm^{-1}: 3460 (hydroxyl) and 1770–1755 (γ-lactone). MS: *m/e* 250 (M^+, 5%), 233 (12), 232 (10) and 43 (100). NMR ($CDCl_3$): δ 1.24 (*d*, 3H, *J* = 6.8 Hz, C_{11}-Me),

1.30 (*s*, 3H, C_4-Me), 1.70 (*br s*, 3H, C_{10}-Me) and 3.81 ppm (*t*, 1H, $J = 8.9$ Hz. C_6-H.)

Acid-catalyzed rearrangement of dihydroparthenolide (**6**) *to dihydromicheliolide* (**15**) *and compressanolide* (**3**). Dihydroparthenolide (**6**, 50 mg) was treated with HCl gas in ether at 0° for 5 min, and H_2O was added. The ether layer was washed with 5% $NaHCO_3$ and H_2O and then dried and evapd. The crude dihydromicheliolide (**15**) and compressanolide (**3**) were separated by prep-TLC. Dihydromicheliolide (**15**) was crystallized from ether; mp 128°, IR ν_{max}^{KBr} cm^{-1} 3480 (OH) and 1760 (γ-lactone). MS: *m/e* 250 (M^+, 5%), 233 (12) 232 (10), and 43 (100). NMR ($CDCl_3$): δ 1.24 (*d*, 3H, $J = 6.9$ Hz, C_{11}-Me), 1.29 (*s*, 3H, C_4-Me). 1.68 (*br s*, 3H, C_{11}-Me) and 3.82 ppm (*t*, 3H, $J = 9.5$ Hz C_6-H). The product was identical with the compound produced by the $NaBH_4$ reduction of **2**. Compressanolide (**3**) was obtained as a colorless oil, IR ν_{max}^{film} cm^{-1}: 1770 (γ-lactone), 1639 and 892 (exo-methylene). MS: *m/e* 250 (M^+, 25%), 232 (70) and 43 (100) NMR ($CDCl_3$): δ 1.24 (*d*, 3H, $J = 6.9$ Hz, C_{11}-Me), 1.29 (*s*, 3H, C_4-Me), 4.05 (*dd*, 1H $J = 9.3$ and 10.8 Hz, C_6-H) and 4.96 ppm (*br s*, 2H, C_{10}=CH_2). The product was identical with natural **3** by comparison of its IR, NMR and MS data.

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