JOC*Article*

Stereoselective Synthesis and Determination of the Cytotoxic Properties of Spicigerolide and Three of Its Stereoisomers

Eva Falomir,[†] Juan Murga,[†] Purificación Ruiz,[†] Miguel Carda,*[,†] and J. Alberto Marco*[,‡]

Departamento de Química Inorgánica y Orgánica, Universidad Jaume I, E-12080 Castellón, Spain, and Departamento de Química Orgánica, Universidad de Valencia, E-46100 Burjassot, Valencia, Spain

Rogelio Pereda-Miranda,[§] Mabel Fragoso-Serrano,[§] and Carlos M. Cerda-García-Rojas[⊥]

Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de Mexico, Ciudad Universitaria, Mexico City 04510, Mexico, and Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apdo. 14-740, Mexico City 07000, Mexico

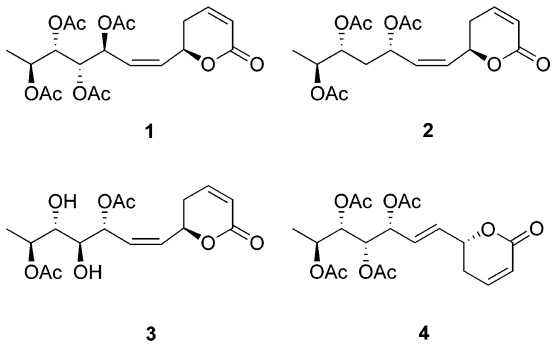
alberto.marco@uv.es

Received April 14, 2003

Stereoselective syntheses of the naturally occurring, cytotoxic lactone spicigerolide and three nonnatural stereoisomers thereof are described. The commercially available sugar L-rhamnose was in all cases the chiral starting material. Key steps in each of these syntheses were asymmetric Brown allylations and ring-closing metatheses. The cytotoxic activities of the four lactones against a range of tumoral lines were then determined.

Lactone rings constitute a structural feature of many natural products.[1,2] A broad range of naturally occurring lactones, particularly those that are Michael acceptors (α,β-unsaturated),[3] display pharmacological properties of interest, e.g. some exhibit antitumoral activity while others are tumor-promoting agents. Examples of such α,β-unsaturated lactones are spicigerolide ((−)-**1**),[4] hyptolide ((+)-**2**),[5] synrotolide ((−)-**3**),[6] and anamarine ((+)-**4**),[7] isolated from several *Hyptis* species and other botanically related genera (Scheme 1). These compounds contain a polyoxygenated chain connected with the α,β-unsaturated lactone moiety and have been found to show a range of pharmacological properties, such as cytotoxicity against human tumor cells, antimicrobial or antifungal activity, etc.[4,8] Pharmacological properties of these types make these compounds interesting synthetic goals. However, efforts in this direction have been limited so far to the syntheses of (+)-**4** and (−)-**4**.[9−11]

SCHEME 1



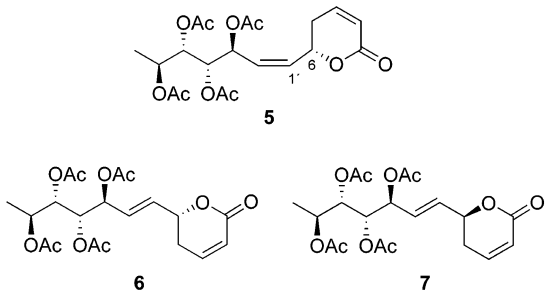
Within our recently initiated program on synthesis of bioactive natural lactones,[12] we have devised a stereoselective syntheses for spicigerolide **1**.[13] Our aim was the preparation of sizable amounts of this lactone to check its cytotoxic activity against a range of tumoral lines.[14]

* To whom correspondence should be addressed.
[†] Universidad Jaume I.
[‡] Universidad de Valencia.
[§] Universidad Nacional Autónoma de Mexico.
[⊥] Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional.

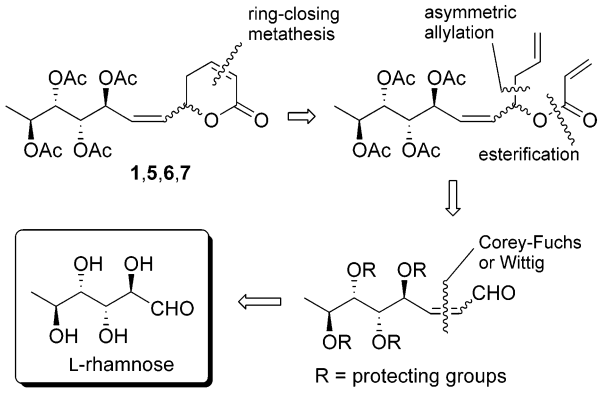
(1) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707−6738.
(2) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377−1395.
(3) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed.* **1985**, *24*, 94−110.
(4) Pereda-Miranda, R.; Fragoso-Serrano, M.; Cerda-García-Rojas, C. M. *Tetrahedron* **2001**, *57*, 47−53.
(5) Achmad, S. A.; Høyer, T.; Kjær, A.; Makmur, L.; Norrestam, R. *Acta Chem. Scand.* **1987**, *41B*, 599−609.
(6) Coleman, M. T. D.; English, R. B.; Rivett, D. E. A. *Phytochemistry* **1987**, *26*, 1497−1499.
(7) Alemany, A.; Márquez, C.; Pascual, C.; Valverde, S.; Martínez-Ripoll, M.; Fayos, J.; Perales, A. *Tetrahedron Lett.* **1979**, *20*, 3583−3586.
(8) Pereda-Miranda, R.; Hernández, L.; Villavicencio, M. J.; Novelo, M.; Ibarra, P.; Chai, H.; Pezzuto, J. M. *J. Nat. Prod.* **1993**, *56*, 583−593.
(9) Lichtenthaler, F.; Lorenz, K.; Ma, W. *Tetrahedron Lett.* **1987**, *28*, 47−50.
(10) Lorenz, K.; Lichtenthaler, F. *Tetrahedron Lett.* **1987**, *28*, 6437−6440.
(11) Valverde, S.; Hernández, A.; Herradón, B.; Rabanal, R. M.; Martín-Lomas, M. *Tetrahedron* **1987**, *43*, 3499−3504.
(12) (a) Carda, M.; Rodríguez, S.; Segovia, B.; Marco, J. A. *J. Org. Chem.* **2002**, *67*, 6560−6563. (b) Carda, M.; González, F.; Castillo, E.; Rodríguez, S.; Marco, J. A. *Eur. J. Org. Chem.* **2002**, 2649−2655. (c) Murga, J.; Falomir, E.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447−3449. (d) Carda, M.; Rodríguez, S.; Castillo, E.; Bellido, A.; Díaz-Oltra, S.; Marco, J. A. *Tetrahedron* **2003**, *59*, 857−864.
(13) For a preliminary report, see: Falomir, E.; Murga, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 539−541. For a stereoselective synthesis of (+)-**2**, see: Murga, J.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Tetrahedron Lett.* **2003**, *44*, 1737−1739.
(14) Spicigerolide was isolated in minute amounts from *Hyptis spicigera*. The available product was consumed in the preliminary cytotoxicity measurements (ref 4).

10.1021/jo034470y CCC: $25.00
Published on Web 06/13/2003

SCHEME 2



SCHEME 3

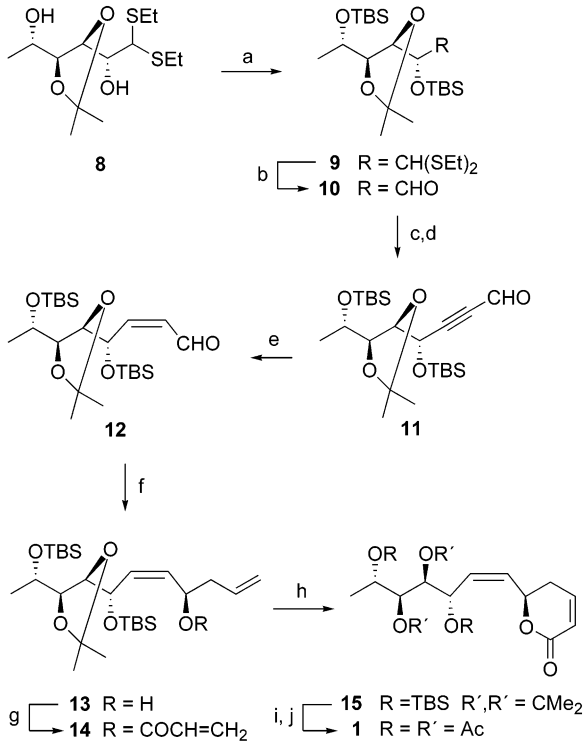


In view of the interesting biological properties of 6-alkenyl-5,6-dihydropyran-2-ones,[15] we further envisaged the preparation of some analogues for studies on structure−activity relationships. Thus, compounds **5**−**7**, stereoisomeric with **1** at the ring-closing lactone carbon (C-6) and/or the nonconjugated $C_{1'}-C_{2'}$ double bond,[16] were selected as further synthetic targets (Scheme 2).

The nature of the polyoxygenated chain of compounds **1**−**4** suggests a sugar as the starting material. In lactone **1** this chain exhibits a configuration coincident with that of the commercially available monosaccharide L-rhamnose, which was thus selected as the starting material. The general retrosynthetic concept designed for **1** and for its analogues **5**−**7** is depicted in Scheme 3. The main difference resides in the method used for the stereoselective creation of the nonconjugated C=C bond. The sequential Corey−Fuchs homologation/formylative rearrangement/Lindlar semihydrogenation protocol was chosen for *Z* olefinations whereas the standard Wittig reaction served to generate *E* olefinic bonds.

The selective manipulation of the aldehyde function of the rhamnose moiety required the introduction of protecting groups into the polyhydroxylated chain.[17] The

SCHEME 4[a]



[a] Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, Δ (84%). (b) $HgCl_2$, $CaCO_3$, aq MeCN, rt (89%). (c) CBr_4, PPh_3, Zn, CH_2Cl_2, 0 °C. (d) *n*-BuLi, −78 °C, then DMF (75% overall for both steps). (e) H_2, Lindlar catalyst (95%). (f) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C (85%, 88:12 diastereoisomeric mixture). (g) Acryloyl chloride, Et_3N, DMAP, CH_2Cl_2, rt (80%). (h) 10% PhCH=RuCl$_2$(PCy$_3$)$_2$, CH_2Cl_2, Δ (86%). (i) PPTS, MeOH, 70 °C. (j) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (61% overall for both steps). Abbreviations: TBS, *tert*-butyldimethylsilyl; Ipc, isopinocamfeyl; DMAP, 4-(dimethylamino)pyridine; Cy = cyclohexyl; PPTS, pyridinium *p*-toluenesulfonate.

starting compound was the known thioacetal **8** (Scheme 4), easily prepared in two steps and 83% overall yield from L-rhamnose.[18] Silylation of diol **8** to compound **9** was performed with *tert*-butyldimethylsilyl triflate.[19] Mercury-promoted hydrolysis of the thioacetal group unveiled the latent aldehyde function to yield **10**, which was then subjected to Corey−Fuchs homologation.[20] Treatment of the resulting dibromomethylene derivative with *n*-BuLi generated an alkynyllithium derivative, which was formylated in situ with DMF. This gave the α,*β*-acetylenic aldehyde **11**, which was semihydrogenated with the aid of Lindlar's catalyst. Asymmetric allylation of the α,*β*-unsaturated aldehyde **12** was unsuccessful with Keck's methodology.[21] However, Brown's protocol[22] proved useful

(15) Lactones with this structural moiety have been found to exhibit potent cytotoxic and/or antifungal properties. Recent examples are fostriecin (Stampwala, S. S.; Bunge, R. H.; Hurley, T. R.; Willmer, N. E.; Brankiewicz, A. J.; Steinman, C. E.; Smitka, T. A.; French, J. C. *J. Antibiot*. **1983**, *36*, 1601−1605), members of the leptomycin family (Kalesse, M.; Christmann, M. *Synthesis* **2002**, 981−1003), and the antifungal pyrones isolated from *Ravensara crassifolia* (Raoelison, G. E.; Terreaux, C.; Queiroz, E. F.; Zsila, F.; Simonyi, M.; Antus, S.; Randriantsoa, A.; Hostettmann, K. *Helv. Chim. Acta* **2001**, *84*, 3470−3476).

(16) This numbering corresponds to the systematic IUPAC nomenclature of spicigerolide as a derivative of 5,6-dihydropyran-2-one bearing a side chain at C-6.

(17) An early introduction of the acetate groups present in the final structure was discarded because of their anticipated instability to some of the planned reaction conditions.

(18) Foster, A. B.; Lehmann, J.; Stacey, M. *J. Chem. Soc.* **1961**, 4649−4653.

(19) Silylation under standard conditions (*tert*-butyldimethylsilyl chloride, DMF, imidazole, 80 °C) caused selective silylation of the hydroxyl group at C-5, leaving the hindered 2-OH untouched.

(20) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769−3772.

(21) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. Almost no reaction was observed after 2 days at −20 °C.

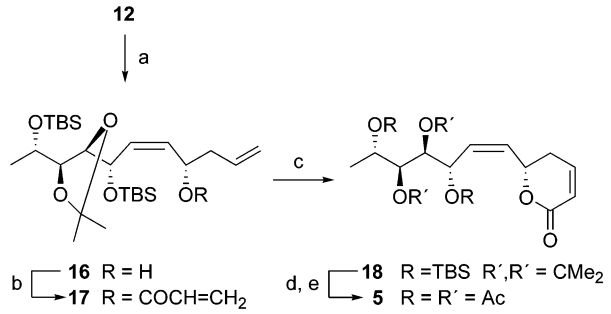
(22) (a) Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 2417−2420. (b) For a very recent review on asymmetric allylborations see: Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23−35.

here. Thus, an allylating reagent (allylBIpc$_2$), prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride), reacted with **12** to afford in good yield the *cis*-allylic alcohol **13**, accompanied by its epimer at the newly formed stereogenic carbon (an 88:12 diastereomeric mixture). Acylation of **13** with acryloyl chloride yielded ester **14**, which could then be easily separated from its diastereoisomer by standard chromatography on silica gel (the indicated yield corresponds to the isolated major diastereoisomer). Ring-closing metathesis (RCM) of acrylate **14** to lactone **15** took place with excellent yield under the catalysis of Grubbs's ruthenium complex PhCH=RuCl$_2$(PCy$_3$)$_2$.[23,24] Finally, hydrolytic cleavage of all three protecting groups, followed by acetylation of the four liberated hydroxyl functions (seven steps altogether) was performed in an excellent 61% overall yield to provide **1**, identical in all its spectral properties with natural spicigerolide.[4]

We then proceeded to synthesize spicigerolide analogues **5**−**7** according to the same main synthetic concept. Aldehyde **12** was thus the starting material for the synthesis of spicigerolide C-6 epimer **5**, as depicted in Scheme 5. Reaction with the allylating reagent prepared from allylmagnesium bromide and (−)-DIP-Cl provided the *cis*-allylic alcohol **16**, which was then transformed into lactone **5** through the same sequence of reactions depicted in Scheme 4 (for analytical data of compounds **5** and **16**−**18**, see the Supporting Information).

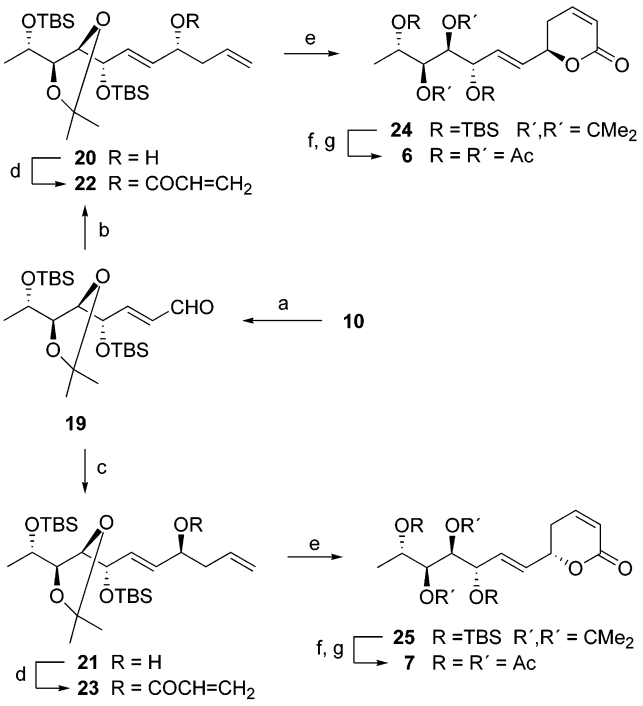
For lactones **6** and **7**, the reaction sequence was appropriately changed to accommodate the creation of the trans $C_{1'}$=$C_{2'}$ bond (Scheme 6). Thus, aldehyde **10** was subjected to Wittig olefination with phosphorane Ph$_3$P=CHCHO to yield the *E* conjugated aldehyde **19**, which was then treated with either of the aforementioned, enantiomeric allylboron reagents. This provided the epimeric homoallylic alcohols **20** and **21**, which were then acylated with acryloyl chloride. RCM of the resulting acrylates, **22** and **23**, furnished lactones **24** and **25**, respectively, which were then transformed into **6** and **7** as described above for the conversion **15** → **1** (for analytical data of compounds **6**, **7**, and **20**−**25**, see the Supporting Information).

SCHEME 5[a]



[a] Reagents and conditions: (a) allylBIpc$_2$ [from (−)-DIP-Cl and allylmagnesium bromide], Et$_2$O, −78 °C (84%, 96:4 diastereoisomeric mixture). (b) Acryloyl chloride, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt (75%). (c) 10% PhCH=RuCl$_2$(PCy$_3$)$_2$, CH$_2$Cl$_2$, Δ (78%). (d) PPTS, MeOH, 70 °C. (e) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt (57% overall for both steps).

SCHEME 6[a]



[a] Reagents and conditions: (a) Ph$_3$P=CHCHO, toluene, 90 °C, 1 h, 80%. (b) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et$_2$O, −78 °C (80% of **20** as a 96:4 diastereoisomeric mixture). (c) allylBIpc$_2$ [from (−)-DIP-Cl and allylmagnesium bromide], Et$_2$O, −78 °C (88% of **21** as a single diastereoisomer). (d) Acryloyl chloride, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt (78% of **22** and 77% of **23**). (e) 10% PhCH=RuCl$_2$(PCy$_3$)$_2$, CH$_2$Cl$_2$, Δ (77% of **24** and 80% of **25**). (f) PPTS, MeOH, 70 °C. (g) Ac$_2$O, Et$_3$N, DMAP, CH$_2$Cl$_2$, rt (46% of **6** and 44% of **7**, overall yields for the two steps).

Cytotoxicity assays were performed as described in the Supporting Information. The results are shown in Table 1. Moderate cytotoxic activities were observed in lactones **1**, **5**, and **6**, but not in **7**, which was essentially inactive. Furthermore, the compounds proved to be selective in their cytotoxic action. Thus, spicigerolide **1** was the most active substance against the nasopharyngeal carcinoma (KB) line but less active against the other tumoral lines. In contrast, the nonnatural analogues **5** and **6** were more active than **1** against the squamous cell cervix carcinoma

(23) (a) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141−8153. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Trnka, T.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(24) RCM reactions have often been used in the course of the synthesis of natural products containing lactone rings. For recent examples, see: Argentilactone: Hansen, T. V. *Tetrahedron: Asymmetry* **2002**, *13*, 547−550. Boronolide: Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513−3516. Ghosh, A. K.; Bilcer, G. *Tetrahedron Lett.* **2000**, *41*, 1003−1006. Epotilones: Nicolaou, K. C.; Ritzén, A.; Namoto, K. *Chem. Commun.* **2001**, 1523−1535. Fostriecin: Wang, Y.-G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615−4618. Fuji, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733−736. Goniodiol: Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547−7550. Banwell, M. G.; Coster, M. J.; Karunaratne, O. P.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1622−1624. Goniothalamin: Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583−586. Laulimalide: Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973−8982. Malyngolide: Mizutani, H.; Watanabe, M.; Honda, T. *Tetrahedron* **2002**, *58*, 8929−8936. Phorboxazoles: Greer, P. B.; Donaldson, W. A. *Tetrahedron* **2002**, *58*, 6009−6018. Peloruside A: Ghosh, A. K.; Kim, J.-H. *Tetrahedron Lett.* **2003**, *44*, 3967−3969. Strictifolione: Tosaki, S.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495−498. Tetrahydrolipstatin: Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743−1744. Umuravumbolide: Reddy, M. V. R.; Rearick, J. P.; Hoch, N.; Ramachandran, P. V. *Org. Lett.* **2001**, *3*, 19−20. Zearalenone: Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990−7995. See also ref 12.

TABLE 1. Cytotoxic Activities of Lactones 1, 5, 6, and 7

	cell tumoral line, ED_{50} (μg/mL)[a]			
compd	HCT-15	UISO	KB	OVCAR
1	17.4	15.9	5.8	19.0
5	18.7	4.3	14.3	19.7
6	>20	5.4	19.3	>20
7	>20	>20	>20	>20

[a] Abbreviations: HCT-15, colon carcinoma; SQC-1 UISO, squamous cell cervix carcinoma; KB, nasopharyngeal carcinoma; OVCAR, ovarian carcinoma.

(UISO) line. None of the compounds showed significant activity against the HCT-15 and OVCAR tumoral lines.

In summary, the naturally occurring lactone spicigerolide **1** has been synthesized for the first time from the commercially available sugar L-rhamnose in 12 operative steps with an overall 15% yield. Three nonnatural spicigerolide analogues **5**−**7** were synthesized via appropriate modifications of the synthetic sequence. In the cytotoxicity assays, three of the compounds showed moderate activity against the nasopharyngeal carcinoma (KB) and the squamous cell cervix carcinoma (UISO) lines. We are currently pursuing stereoselective syntheses of other structurally related lactones such as **2**−**4** to evaluate their cytotoxic activities. When a broader range of lactones of this structural type becomes available for biological evaluation, it will be possible to draw deeper conclusions about the relation between structure and activity. Work in this direction is underway and will be published in due course.

Experimental Section

4-[1-(*tert*-Butyldimethylsilyloxy)-2,2-bis(ethylsulfanyl)-ethyl]-5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolane (9). Diol **8**[18] (1.86 g, 6 mmol) was dissolved under N_2 at room temperature in anhydrous CH_2Cl_2 (40 mL) and treated with 2,6-lutidine (2.1 mL, 18 mmol) and *tert*-butyldimethylsilyl triflate (3.1 mL, 13.5 mmol) (both reagents added neat via syringe). The resulting solution was heated at reflux for 18 h, then poured into satd aq NH_4Cl and worked up (CH_2Cl_2). Column chromatography on silica gel (hexanes−EtOAc, 19:1) yielded the disilylated derivative **9** (2.71 g, 84%) as a colorless oil: $[\alpha]_D$ −10.2 (*c* 1.8; $CHCl_3$). ^{1}H NMR (500 MHz) δ 4.46 (1H, dd, J = 9, 2 Hz), 4.14 (1H, d, J = 1 Hz), 3.96 (2H, m), 3.82 (1H, dq, J = 8, 6 Hz), 2.71 (2H, m), 2.61 (2H, m), 1.38 (6H, s), 1.27 (3H, t, J = 7 Hz), 1.26 (3H, t, J = 7 Hz), 1.22 (3H, d, J = 6 Hz), 0.93 (9H, s), 0.91 (9H, s), 0.24 (3H, s), 0.16 (3H, s), 0.13 (3H, s), 0.08 (3H, s); ^{13}C NMR (125 MHz) δ 109.8, 18.5, 18.0 (C), 83.1, 79.3, 76.7, 68.8, 54.9 (CH), 25.9, 25.5 (CH_2), 29.4, 29.3, 26.3, 26.2, 20.4, 14.5, 14.4, −3.6, −4.0, −4.3, −4.6 (CH_3). HR EIMS *m*/*z* (rel intensity) 481.2300 [M^+ − *t*Bu] (22), 423 (25), 345 (35), 159 (100), 73 (43). Calcd for $C_{25}H_{54}O_4S_2Si_2$ − *t*Bu, 481.2298. Anal. Calcd for $C_{25}H_{54}O_4S_2Si_2$: C, 55.71; H, 10.10. Found: C, 55.81; H, 10.00.

1-(*tert*-Butyldimethylsilyloxy)-1-{5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-acetaldehyde (10). Thioacetal **9** (2.7 g, 5 mmol) was dissolved at room temperature in a 5:1 acetonitrile/water mixture (90 mL) and treated with $CaCO_3$ (2.25 g, 22.5 mmol) and $HgCl_2$ (5.43 g, 20 mmol). The resulting solution was stirred at room temperature for about 1 h (**TLC monitoring!**), then filtered through Celite. The Celite pad was washed with EtOAc, the combined organic layers were evaporated under reduced pressure, and the aqueous residue was saturated with NaI and extracted with EtOAc. The combined organic layers were finally washed again with satd aq NaI, dried on anhydrous Na_2SO_4, and evaporated under reduced pressure. This gave an oily residue that was chromatographed on silica gel (hexanes−EtOAc, 19:1) to furnish aldehyde **10** (1.92 g, 89%) as a colorless oil: $[\alpha]_D$ +2.1 (*c* 4; $CHCl_3$). ^{1}H NMR (500 MHz) δ 9.64 (1H, d, J = 2 Hz), 4.24 (1H, dd, J = 6.5, 3.7 Hz), 4.13 (1H, dd, J = 3.7, 2 Hz), 3.95 (1H, dd, J = 6.5, 5.5 Hz), 3.88 (1H, dq, J = 5.5, 6 Hz), 1.37 (6H, s), 1.18 (3H, d, J = 6 Hz), 0.93 (9H, s), 0.88 (9H, s), 0.10 (3H, s), 0.09 (3H, s), 0.06 (6H, s); ^{13}C NMR (125 MHz) δ 109.4, 18.2, 18.1 (C), 202.0, 81.1, 79.1, 78.3, 68.8 (CH), 27.5, 27.4, 25.9, 25.8, 20.5, −4.3, −4.4, −4.6, −4.7 (CH_3). IR (NaCl) 1739 (C=O) cm^{-1}. HR EIMS *m*/*z* (rel intensity) 417.2485 [M^+ − Me] (2), 403 (4), 159 (100), 73 (35). Calcd for $C_{21}H_{44}O_5Si_2$ − Me, 417.2492. Anal. Calcd for $C_{21}H_{44}O_5Si_2$: C, 58.29; H, 10.25. Found: C, 58.40; H, 10.40.

4-(*tert*-Butyldimethylsilyloxy)-4-{5-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl[1,3]dioxolan-4-yl}-but-2-ynal (11). Carbon tetrabromide (4 g, ca. 12 mmol) and triphenylphosphine (4.2 g, 16 mmol) were added under N_2 to an ice-cooled suspension of Zn dust (261 mg, 4 mmol) in dry CH_2Cl_2 (40 mL). After the mixture was stirred for 1 h, a solution of aldehyde **10** (1.73 g, 4 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise. The resulting solution was further stirred at 0 °C for 2 h, then diluted with hexanes (50 mL) and allowed to stand. The orange-reddish precipitate was separated by means of filtration, dissolved in CH_2Cl_2 (10 mL), diluted again with hexanes (35 mL), and allowed to stand. This operation was repeated twice more. The organic layers were then combined, evaporated under reduced pressure, redissolved in a 9:1 hexanes−Et_2O mixture (45 mL), and filtered through Celite. After evaporation in vacuo, the oily residue was used directly in the next transformation.

The crude dibromomethylene derivative from the previous reaction was dissolved under N_2 in dry THF (45 mL) and cooled to −78 °C. A 1.6 M solution of *n*-BuLi in hexanes (5 mL, 8 mmol) was then added dropwise via syringe. The bath temperature was allowed to reach −20 °C and the mixture was stirred for 1 h. After this time, dry DMF (2.7 mL, 35 mmol) was added dropwise, the bath temperature was allowed to reach 0 °C, and the mixture was stirred for 2 h. After quenching with satd aq NH_4Cl (5 mL), the mixture was worked up (EtOAc). Column chromatography on silica gel (hexanes−EtOAc, 19:1) provided aldehyde **11** (1.37 g, 75% overall yield from **7**) as a colorless oil; $[\alpha]_D$ +10.7 (*c* 2.3; $CHCl_3$). ^{1}H NMR (500 MHz) δ 9.22 (1H, s), 4.67 (1H, d, J = 4.2 Hz), 4.07 (1H, dd, J = 6, 4.2 Hz), 3.89 (1H, quint, J = 6 Hz), 3.81 (1H, t, J = 6 Hz), 1.39 (3H, s), 1.37 (3H, s), 1.20 (3H, d, J = 6 Hz), 0.90 (9H, s), 0.87 (9H, s), 0.16 (3H, s), 0.13 (3H, s), 0.06 (6H, s); ^{13}C NMR (125 MHz) δ 110.1, 94.6, 85.0, 18.1, 18.0 (C), 175.8, 82.1, 81.1, 69.4, 65.1 (CH), 27.8, 27.6, 25.8, 25.7, 20.3, −4.3, −4.4, −4.5, −4.8 (CH_3). IR (NaCl) 1721 (C=O) cm^{-1}. HR EIMS *m*/*z* (rel intensity) 441.2505 [M^+ − Me] (12), 399 [M^+ − *t*Bu] (26), 341 (54), 197 (63), 159 (93), 73 (100). Calcd for $C_{23}H_{44}O_5Si_2$ − Me, 441.2492. Anal. Calcd for $C_{23}H_{44}O_5Si_2$: C, 60.48; H, 9.71. Found: C, 60.40; H, 9.91.

(4*S*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(4*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl[1,3]-dioxolan-4-yl}-but-2*Z*-enal (12). A suspension of commercial Lindlar catalyst (5% Pd on $CaCO_3$, 200 mg) in CH_2Cl_2 (8 mL) was stirred for 10 min under an H_2 atmosphere. A solution of aldehyde **11** (1.14 g, 2.5 mmol) in CH_2Cl_2 (15 mL) was then added dropwise via syringe. The resulting solution was further stirred at room temperature until consumption of the starting material (about 3 h, **TLC monitoring!**). The reaction mixture was then filtered through Celite, the organic layer was evaporated under reduced pressure, and the oily residue was chromatographed on silica gel (hexanes−EtOAc, 19:1) to yield the α,*β*-unsaturated aldehyde **12** (1.09 g, 95%) as a colorless oil: $[\alpha]_D$ −6.8 (*c* 2.2; $CHCl_3$). ^{1}H NMR (500 MHz) δ 10.10 (1H, d, J = 7.7 Hz), 6.55 (1H, dd, J = 11.5, 9 Hz), 6.06 (1H, dd, J = 11.5, 7.7 Hz), 5.06 (1H, dd, J = 9, 5 Hz), 4.07 (1H, dd, J = 6, 5 Hz), 3.88 (1H, quint, J = 6 Hz), 3.77 (1H, t, J = 6 Hz), 1.38 (3H, s), 1.37 (3H, s), 1.20 (3H, d, J = 6 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.11 (3H, s), 0.10 (3H, s), 0.09 (3H, s), 0.07 (3H, s); ^{13}C NMR (125 MHz) δ 109.8, 18.1, 18.0 (C), 191.1, 150.2,

130.4, 82.4, 81.6, 69.7, 69.6 (CH), 27.8, 27.7, 25.9, 25.8, 20.7, −4.1, −4.2, −4.3, −4.4 (CH_3). IR (NaCl) 1725, 1700 (C=O) cm^{-1}. HR EIMS *m/z* (rel intensity) 443.2649 [M^+ − Me] (1), 215 (24), 159 (100), 73 (74). Calcd for $C_{23}H_{46}O_5Si_2$ − Me, 443.2649. Anal. Calcd for $C_{23}H_{46}O_5Si_2$: C, 60.21; H, 10.11. Found: C, 60.33; H, 10.00.

(4*R*,5*Z*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-7-{(4*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-hepta-1,5-dien-4-ol (13). Allylmagnesium bromide (commercial 1 M solution in Et_2O, 2.5 mL, 2.5 mmol) was added dropwise under N_2 via syringe to a solution of (+)-diisopinocampheylboron chloride (962 mg, 3 mmol) in dry Et_2O (20 mL) cooled in a dry ice−acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. The solution was then allowed to stand, which caused precipitation of magnesium chloride. The supernatant solution was then carefully transferred to another flask via cannula. After this flask was cooled at − 78 °C, a solution of aldehyde **12** (917 mg, 2 mmol) in dry Et_2O (10 mL) was added dropwise via syringe. The resulting solution was further stirred at the same temperature. for 5 h. The reaction mixture was then quenched through addition of phosphate pH 7 buffer solution (8 mL), MeOH (12 mL), and 30% H_2O_2 (8 mL). After being stirred for 30 min, the mixture was poured onto satd aq $NaHCO_3$ and worked up as usual (Et_2O). Column chromatography on silica gel (hexanes−EtOAc, 9:1) afforded alcohol **13** (851 mg, 85%) as an 88:12 mixture of epimers (the major one indicated in Scheme 4). This mixture was used as such in the next step (NMR signals are those of the major isomer): ^1H NMR (500 MHz) δ 5.80 (1H, m), 5.63 (1H, dd, J = 11, 9 Hz), 5.52 (1H, dd, J = 11, 9 Hz), 5.15−5.05 (2H, m), 4.52 (1H, dd, J = 9,7 Hz), 4.32 (1H, dt, J = 9, 7 Hz), 4.00−3.90 (2H, m), 3.78 (1H, t, J = 7 Hz), 2.80 (1H, br s), 2.40−2.25 (2H, m), 1.44 (3H, s), 1.39 (3H, s), 1.19 (3H, d, J = 6 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.08 (6H, s), 0.07 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz) δ 109.5, 18.2, 18.1 (C), 135.0, 134.1, 133.6, 83.2, 80.1, 70.8, 69.4, 66.2 (CH), 117.6, 40.9 (CH_2), 27.6, 27.2, 26.0 (2×), 19.6, −4.0, −4.1, −4.2, −4.3 (CH_3). IR (NaCl) 3490 (br, OH) cm^{-1}. HR EIMS *m/z* (rel intensity) 485.3114 [M^+ − Me] (2), 367 (8), 295 (9), 253 (20), 241 (20), 224 (16), 159 (100). Calcd for $C_{26}H_{52}O_5Si_2$ − Me, 485.3118.

(1*R*,2*Z*,4*S*)-1-Allyl-4-(*tert*-butyldimethylsilyloxy)-4-{(4*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl[1,3]dioxolan-4-yl}-but-2-enyl Acrylate (14). Alcohol **13** (epimer mixture) from above was dissolved in dry CH_2Cl_2 (20 mL), cooled to 0 °C, and treated under N_2 at this temperature with triethylamine (560 μL, 4 mmol), acryloyl chloride (285 μL, 3.5 mmol), and DMAP (25 mg, ca. 0.2 mmol). The mixture was then stirred at room temperature for 4 h, poured onto satd aq NH_4Cl, and worked up (CH_2Cl_2). Column chromatography on silica gel (hexanes−EtOAc, 19:1) furnished acrylate **14** (755 mg, 80%) as a single diastereoisomer: colorless oil; $[\alpha]_D$ −7.2 (*c* 1.3; $CHCl_3$). ^1H NMR (500 MHz) δ 6.39 (1H, dd, J = 17.5, 1 Hz), 6.10 (1H, dd, J = 17.5, 10.5 Hz), 5.81 (1H, dd, J = 10.5, 1 Hz), 5.77 (1H, m), 5.66−5.52 (3H, m), 5.15−5.10 (2H, m), 4.70 (1H, dd, J = 8.8, 3 Hz), 3.98 (1H, dd, J = 7, 3 Hz), 3.95−3.85 (2H, m), 2.45 (2H, m), 1.39 (3H, s), 1.37 (3H, s), 1.17 (3H, d, J = 6 Hz), 0.91 (18H, s), 0.11 (3H, s), 0.09 (3H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (125 MHz) δ 164.9, 109.0, 18.2, 18.1 (C), 134.0, 132.6, 128.6, 128.5, 81.4, 80.9, 69.8, 69.5, 69.4 (CH), 130.6, 118.4, 39.2 (CH_2), 27.5, 27.4, 26.0, 25.9, 19.4, −4.1, −4.2, −4.3, −4.4 (CH_3). IR (NaCl) 1727 (C=O) cm^{-1}. HR EIMS *m/z* (rel intensity) 539.3229 [M^+ − Me] (2), 367 (14), 295 (18), 224 (18), 159 (100), 129 (28), 73 (46). Calcd for $C_{29}H_{54}O_6Si_2$ − Me, 539.3224. Anal. Calcd for $C_{29}H_{54}O_6Si_2$: C, 62.77; H, 9.81. Found: C, 62.59; H, 10.00.

(6*R*)-6-[(3*S*)-3-*tert*-Butyldimethylsilyloxy-3-{(4*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-prop-1*Z*-enyl)]-5,6-dihydropyran-2-one (15). Acrylate **14** (416 mg, 0.75 mmol) and Grubbs' complex PhCH=$RuCl_2(PCy_3)_2$ (62 mg, 0.075 mmol) were dissolved in dry, degassed CH_2Cl_2 (75 mL) and heated under N_2 at reflux until consumption of the starting material (3−4 h, **TLC monitoring!**). Solvent removal under reduced pressure was followed by column chromatography on silica gel (hexanes−EtOAc, 4:1) to yield α,β-unsaturated lactone **15** (340 mg, 86%) as a colorless oil: $[\alpha]_D$ −20.4 (*c* 1.3; $CHCl_3$). ^1H NMR (500 MHz) δ 6.88 (1H, m), 6.04 (1H, br d, J = 9.7 Hz), 5.79 (1H, dd, J = 11.4, 8.5 Hz), 5.70 (1H, dd, J = 11.4, 9.2 Hz), 5.30 (1H, m), 4.60 (1H, dd, J = 8.5, 3.3 Hz), 4.01 (1H, dd, J = 7.2, 3.3 Hz), 3.86 (1H, dq, J = 6.5, 6 Hz), 3.76 (1H, dd, J = 7.2, 6.5), 2.43 (2H, m), 1.37 (3H, s), 1.36 (3H, s), 1.21 (3H, d, J = 6 Hz), 0.89 (18H, s), 0.08 (3H, s), 0.07 (6H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz) δ 163.4, 109.1, 18.2, 18.1 (C), 144.3, 134.7, 127.8, 121.7, 82.3, 81.3, 73.9, 70.0, 69.9 (CH), 29.7 (CH_2), 27.5, 27.4, 26.0, 25.8, 20.6, −3.9, −4.2, −4.3 (CH_3). IR (NaCl) 1733 (C=O) cm^{-1}. HR EIMS *m/z* (rel intensity) 511.2908 [M^+ − Me] (8), 469 (54), 411 (22), 367 (30), 267 (48), 159 (100), 129 (28), 73 (36). Calcd for $C_{27}H_{50}O_6Si_2$ − Me, 511.2911. Anal. Calcd.for $C_{27}H_{50}O_6Si_2$: C, 61.55; H, 9.57. Found: C, 61.58; H, 9.49.

(6*R*)-6-[(1*Z*,3*S*,4*S*,5*S*,6*S*)-(3,4,5,6-Tetraacetoxyhept-1-enyl)]-5,6-dihydropyran-2-one, Spicigerolide (1). A solution of unsaturated lactone **15** (263 mg, 0.5 mmol) was dissolved in MeOH (10 mL) and poured into a solution of PPTS (12 mg, 0.05 mmol) in water (100 mL). The resulting solution was heated at 70 °C for 18 h, then brought to neutrality by careful addition of $CaCO_3$, filtered, and evaporated under reduced pressure. The oily residue was then dissolved in dry CH_2Cl_2 (20 mL) and treated under N_2 at room temperature with triethylamine (560 μL, 4 mmol), acetic anhydride (283 μL, 3 mmol), and DMAP (6 mg, 0.05 mmol). The mixture was then stirred for 4 h, poured onto satd aq NH_4Cl, and worked up (CH_2Cl_2). Column chromatography on silica gel (hexanes−EtOAc, 7:3) provided (−)-spicigerolide **1** (130 mg, 61%) as a colorless oil: $[\alpha]_{589}$ −23, $[\alpha]_{578}$ −24, $[\alpha]_{546}$ −27, $[\alpha]_{436}$ −41, $[\alpha]_{365}$ −46 (*c* 2.26; $CHCl_3$). CD, ^1H NMR, and ^{13}C NMR spectra were identical with those of the original sample.[4] HR EIMS *m/z* (rel intensity) 427.1591 [M + H^+] (3), 367 (16), 231 (38), 204 (40), 178 (79), 136 (100). Calcd for $C_{20}H_{27}O_{10}$, 427.1604.

(4*S*)-4-(*tert*-Butyldimethylsilyloxy)-4-{(4*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl[1,3]-dioxolan-4-yl}-but-2*E*-enal (19). Aldehyde **10** (1.73 g, 4 mmol) and triphenylphosphoranylideneacetaldehyde (1.46 g, 4.8 mmol) were dissolved under N_2 in dry toluene (30 mL). The resulting solution was heated at 90 °C for 1 h. The reaction mixture was then worked up (EtOAc), and the oily residue was chromatographed on silica gel (hexanes−EtOAc, 4:1) to yield the α,β-unsaturated aldehyde **19** (1.47 g, 80%) as a colorless oil: $[\alpha]_D$ −16.7 (*c* 1.6; $CHCl_3$). ^1H NMR (500 MHz) δ 9.60 (1H, d, J = 7.8 Hz), 6.90 (1H, dd, J = 15.8, 5.3 Hz), 6.29 (1H, dd, J = 15.8, 7.8 Hz), 4.46 (1H, dd, J = 5.5, 5 Hz), 4.03 (1H, t, J = 5 Hz), 3.85−3.80 (2H, m), 1.38 (3H, s), 1.37 (3H, s), 1.18 (3H, d, J = 6 Hz), 0.92 (9H, s), 0.89 (9H, s), 0.11 (3H, s), 0.06 (6H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz) δ 109.8, 18.2, 18.1 (C), 193.2, 156.4, 132.6, 82.6, 81.2, 73.0, 69.1 (CH), 28.2, 28.1, 25.9, 25.8, 20.4, −4.2, −4.3, −4.4, −4.5 (CH_3). IR (NaCl) 1698 (C=O) cm^{-1}. HR EIMS *m/z* (rel intensity) 443.2639 [M^+ − Me] (3), 401 (8), 199 (44), 159 (100), 73 (90). Calcd for $C_{23}H_{46}O_5Si_2$ − Me, 443.2649. Anal. Calcd for $C_{23}H_{46}O_5Si_2$: C, 60.21; H, 10.11. Found: C, 60.03; H, 10.28.

Acknowledgment. The Spanish authors acknowledge financial support by the Ministry of Science and Technology (project BQU2002-00468) and by Fundació Caixa Castellò-Universidad Jaume I (project PI-1B2002-06). J.M. further thanks the Spanish Ministry of Science and Technology for a Ramón y Cajal fellowship. The Mexican authors thank the UNAM (Dirección General de Asuntos del Personal Académico, project IN200902-2) for financial support.

Supporting Information Available: Tabulated analytical data of compounds **5**−**7**, **16**−**18**, and **20**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034470Y