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Enantiospecific Syntheses of the Potent Bioactives Nagilactone F and the Mould Metabolite LL-Z1271α An Evaluation of their Allelopathic Potential

Alejandro F. Barrero[a*], Juan F. Sánchez[a], Jamal Elmerabet[a], David Jiménez-González[a], Francisco A. Macías[b] and Ana M. Simonet[b].

[a] *Departamento de Química Orgánica, Instituto de Biotecnología, Facultad de Ciencias, Universidad de Granada, Campus Fuentenueva s/n, 18071-Granada (Spain).*
[b] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, C/ República Saharaui s/n, Apdo 40, 11510-Puerto Real, (Cádiz, Spain).*

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Abstract

Improved syntheses are described for nagilactone F and the antibiotic LL-Z1271α, two of the most potent bioactive members of the podolactone family. The allelopathic potential of some members of this podolactone series has been evaluated, with the result that the metabolite LL-Z1271α is one of the most active compounds.

Keywords: podolactones; synthesis; herbicides.

1. Introduction

Podolactones and other related compounds of natural origin show a wide variety of biological activities, including plant growth inhibitory activity, termiticidal activity, insect toxicity, antitumor and antibiotic activities, etc [1-3]. Due to this biological activity, some methods for their preparation have been described [4-8]. We wish to report herein [9] the improved syntheses of nagilactone F (**28**) and LL-Z1271α (**25**), two of the most active members of the family, and also a study on the allelopathic activity of several compounds obtained when developing the synthetic procedure.

2. Results and discussion

These syntheses begin with communic acids, natural substances which are by-products of the production of the essential oil of *Juniperus communis* employed in the manufacture of gin and which have two of the four rings and three of the asymmetric carbons with the same configuration of the target compounds **25** and **28**. Scheme 1 shows the retrosynthetic approach,

* e-mail: afbarre@goliat.ugr.es; Fax number: 34 958 243318

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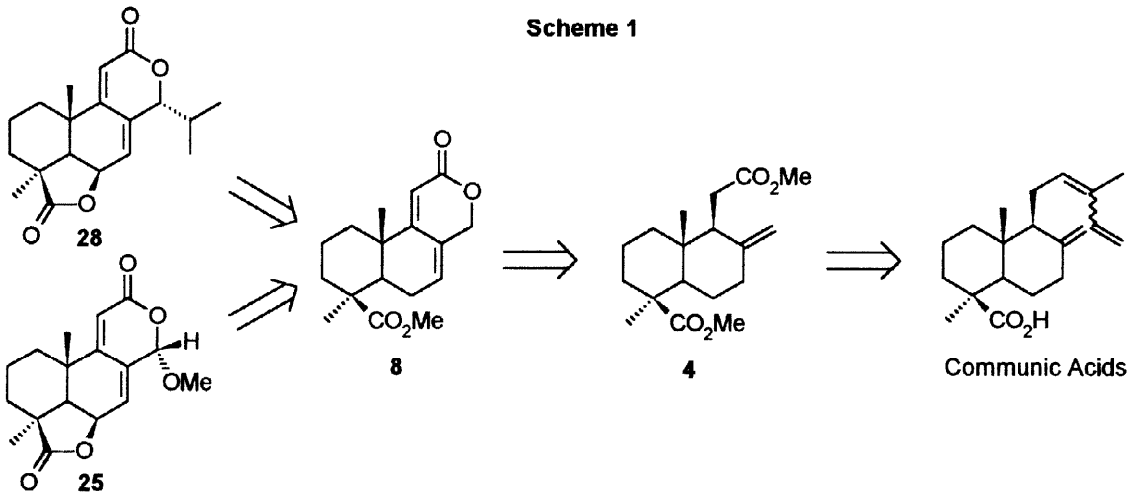
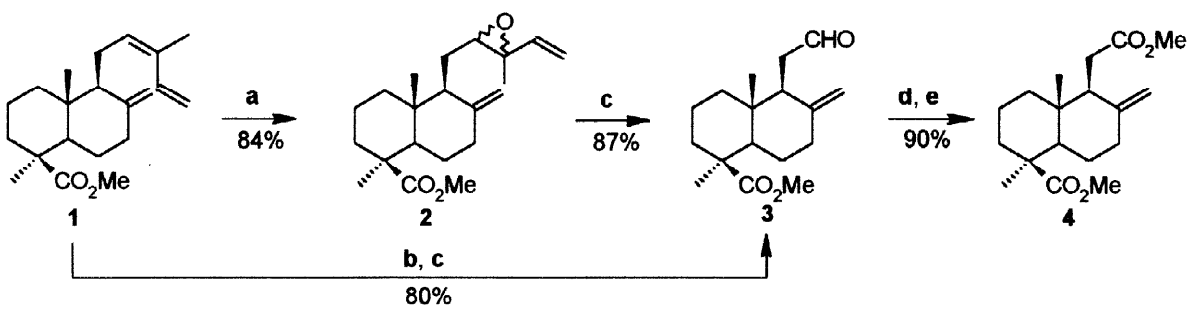
where the key steps are based on δ-lactonization in order to form the C ring, γ-lactonization, 14-hydroxylation and finally, alkylation or O-methylation in that position.

Scheme 1



The aldehyde **3** (Scheme 2), previously obtained by ozonolysis of the methyl ester of cis-communic acid **1** (42 % yield) [10], is prepared with a higher yield (84%) by oxidation of the latter with *m*-CPBA (giving a mixture of α and β epoxides **2**) and subsequent treatment with HIO_4 (87% yield). These epoxides had been previously obtained at a much lower yield (45%) [11]. **3** was also obtained by potassium permanganate oxidation, which led to a mixture of diastereomeric 12,13-diols, and subsequent periodic degradation (80%). Oxidation of **3** [12] and later esterification with diazomethane gave the diester **4** at 90% yield.

Scheme 2

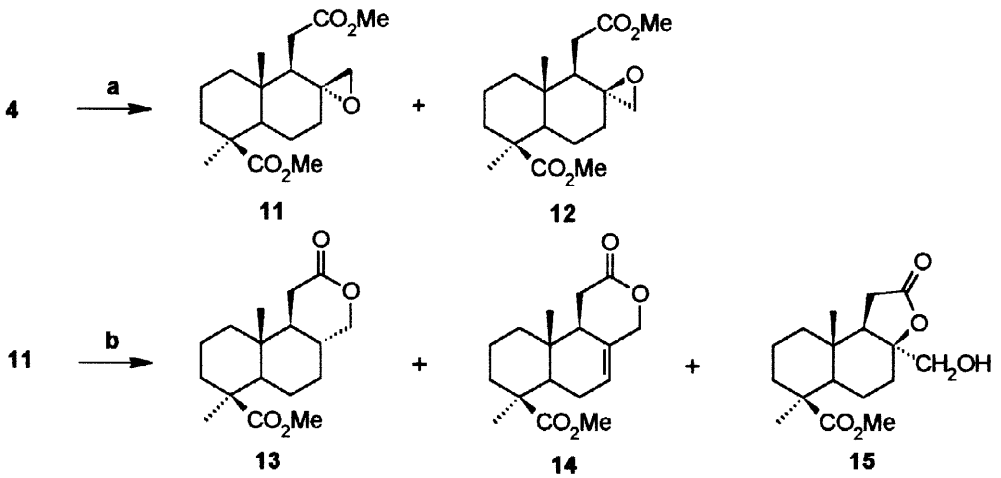


(a) *m*-CPBA, $CH_2Cl_2/NaHCO_3$, -10-0°C; (b) $KMnO_4$, EtOH; (c) HIO_4, THF, rt; (d) $CrO_3/H_2SO_4/H_2O$, acetone; (e) CH_2N_2, Et_2O.

Formation of the δ-lactone **7** from the diester **4** was initially approached by epoxidation of **4** followed by the opening of the epoxides with Lewis or protic acids (Scheme 3). Treatment of **4** with *m*-CPBA gave, in a practically quantitative yield, a mixture of 85:15 of the epoxide **11** together with its β isomer **12**. The configuration indicated for the epimeric epoxides was established with regard to the displacements of the signals assigned to C-14 in the ^{13}C NMR spectrum by comparison with other related epoxides [13]. The opening of the major α-epoxide **11** was initially achieved with $Al(OiPr)_3$ under reflux in toluene, with the δ-lactone **13** turning out to be the major product (71% yield). The configuration of **13** at C-8 was established through the coupling constants between H8-H14. Compounds **14** and the γ-lactone **15** (5% and 11% yield respectively) were also obtained. The formation of **13** can be explained through the

stereospecific rearrangement of the oxirane **11** to the 8α-formyl derivative followed by reduction of the formyl group to primary alcohol (Figure 1). Minor compounds **15** and **14** resulted from the opening of the oxirane ring and subsequent hydrolysis and H-7 elimination, respectively.

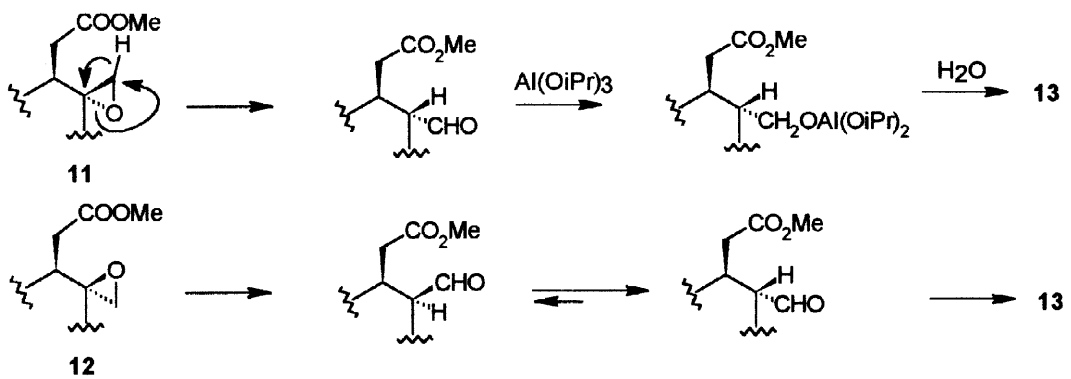
Scheme 3



(a) *m*-CPBA, CH_2Cl_2, 85% for **11**, 15% for **12**;
(b) $Al(iPrO)_3$, 71% for **13**, 5% for **14**, 11% for **15**.

When we carried out the opening of the β-epoxide **12** under the same conditions, the reaction was slower and after 24 hours under reflux in toluene it yielded **13** (20%) and **14** (56%). This different reactivity is attributed to the steric hindrance of coordinating the aluminium reagent to the β-oxirane. On the other hand, the stereochemistry of **13** at C-8 is the result of initial rearrangement to the 8β-formyl derivative followed by isomerization to the more stable 8α-formyl derivative in the basic reaction medium and subsequent reduction (Figure 1).

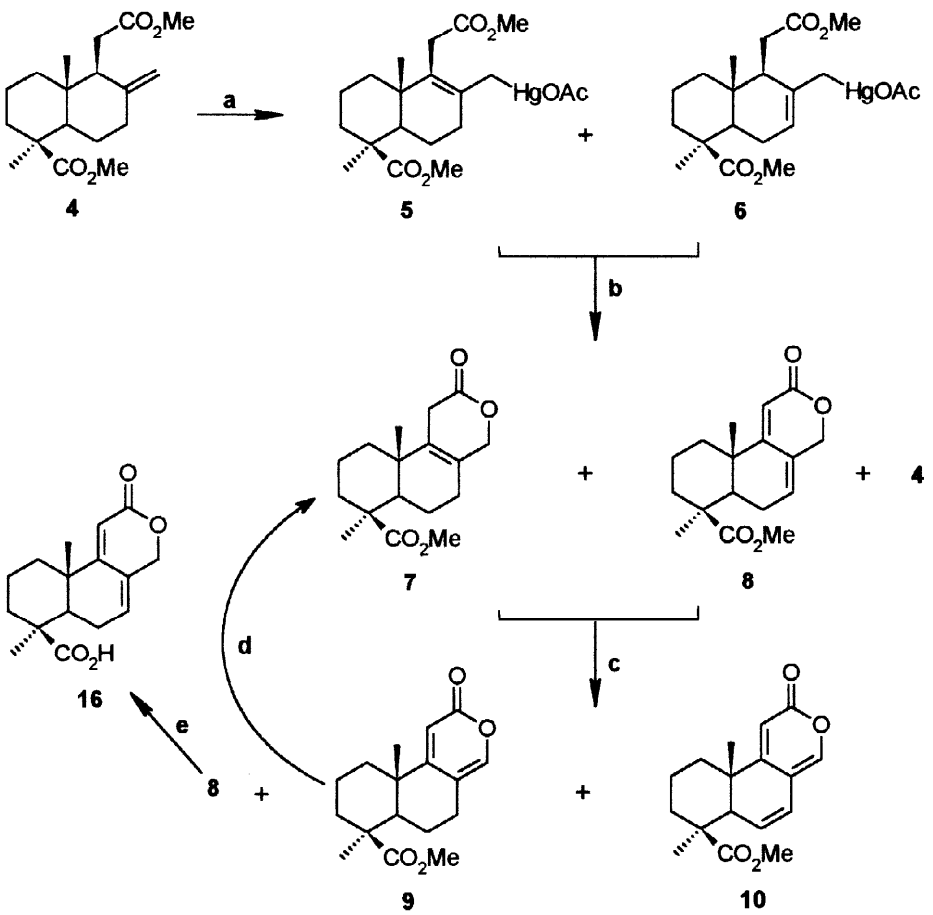
Figure 1



Furthermore, opening of the mixture of both epoxides and subsequent lactonization to **7** (75%) and **14** (8%) could be achieved under reflux with *p*-toluenesulfonic acid (PTSA) in benzene. The transformation was followed by TLC until all the epoxide was consumed. In preliminary assays at lower temperatures, when the reaction was stopped before the epoxides were totally consumed, variable quantities of γ-lactone **15** and its 8-epimer **15'**, resulting from the opening of **11** and later hydroxylation, were also formed during the work-up. Under the same conditions the isomer **12** remained unaltered. The great difference in reactivity between both epimers is

emphasized since the latter needs high temperatures for hydrolysis and the former reacts at room temperature.

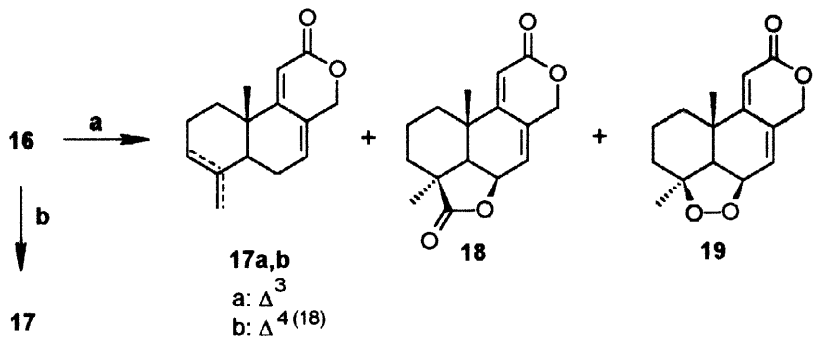
Scheme 4



(a) $Hg(OAc)_2$, toluene, reflux, 100%; (b) $NaBH_4$, O_2, DMF, 75% for **7**, 15% for **8**, 5% for **4**;
(c) DDQ,PTSA, dioxane, reflux, 75%; (d) $NaBH_4$, NaOH, THF, reflux, 87%;
(e) H_2SO_4, rt, 100%.

The formation of δ-lactone **7** (Scheme 4) was also achieved taking into account the fact that, as previously noted [14], the mercuriation reaction in $\Delta^{8(17)}$ of communic acids takes place with loss of the neighboring H-9 hydrogen giving rise to the isomerization of the exocyclic double bond. With this in mind, **4** was refluxed with two equivalents of mercuric acetate affording **5** and **6** as an 8:1 mixture in a quantitative yield. This mixture was reduced with $NaBH_4$/DMF in the presence of an excess of bubbling O_2, producing lactone **7** (75%), dienolide **8** (15%) and the starting product **4** (5%). The dehydrogenation of this mixture was achieved at a 75% yield using DDQ and PTSA to give **8**, **9** and **10** with a ratio of 8:3:1. The yield of the reaction of **7** with DDQ to obtain **8** may be improved by treating **9** with NaOH and $NaBH_4$, recovering the starting product **7** in a very good yield (87%). This reaction implies that opening of the α-pyrone ring, reduction of the α,β unsaturated aldehyde intermediate and cyclisation to lactone occurs. In order to prepare the γ-lactone ring present in the final products, the methyl ester **8**, was transformed into the free acid **16** by treatment with concentrated sulfuric acid, after an unsuccessful hydrolysis assay with diphenyldiselenide/Na [15].

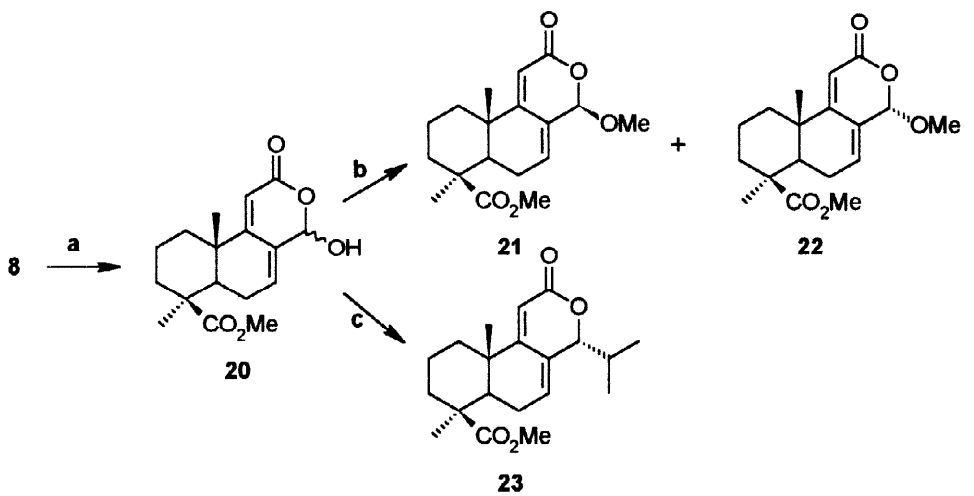
Scheme 5



(a) $Pb(OAc)_4$, hν, benzene, 6% for **17**, 50% for **18**, 12% for **19**;
(b) $PhI(OAc)_2$, I_2, 38%.

With the aim of closing the ring D, compound **16** was treated with iodosobenzene diacetate-iodine system and this yielded a complex mixture from which compounds **17**, resulting from decarboxylation of **16**, could be identified (Scheme 5). Alternatively, treatment of **16** with lead tetraacetate under an argon atmosphere [4] gave the known product **18** at a 50% yield in addition to the by-products **17** (6%) and **19** (12%), which resulted from decarboxylation at C-4 with the loss of hydrogen or trapping of the radical by traces of oxygen which may exist in the reaction medium.

Scheme 6



(a) SeO_2, dioxane, reflux, 90%; (b) MeOH, H_2SO_4, rt, 95%; (c) i-PrMgBr, THF, 0°C, 82%

The introduction of different derivatives at C-14 in **18** was optimized using **8** as a model. The oxidation of this substance with selenium dioxide (Scheme 6) gave the relatively unstable hydroxylactone **20** (90%) as a mixture of α and β epimers, whose equilibrium composition depended on the solvent. Reaction of **20** with isopropylmagnesium bromide took place with high yield (82%) and in a highly stereoselective manner to the α epimer **23**. Treatment of **20** with methanol in acid conditions produced a 95% yield of a mixture (55:45) of β and α-methylated derivatives (**21** and **22**).

Once appropriate conditions for the final steps of the synthesis were established, the dilactone **18** was converted into the δ–hydroxylactone **24** (85% yield) and 15% of the starting compound by reaction with 3 moles of selenium dioxide (Scheme 7). **24** shows identical properties to LL-

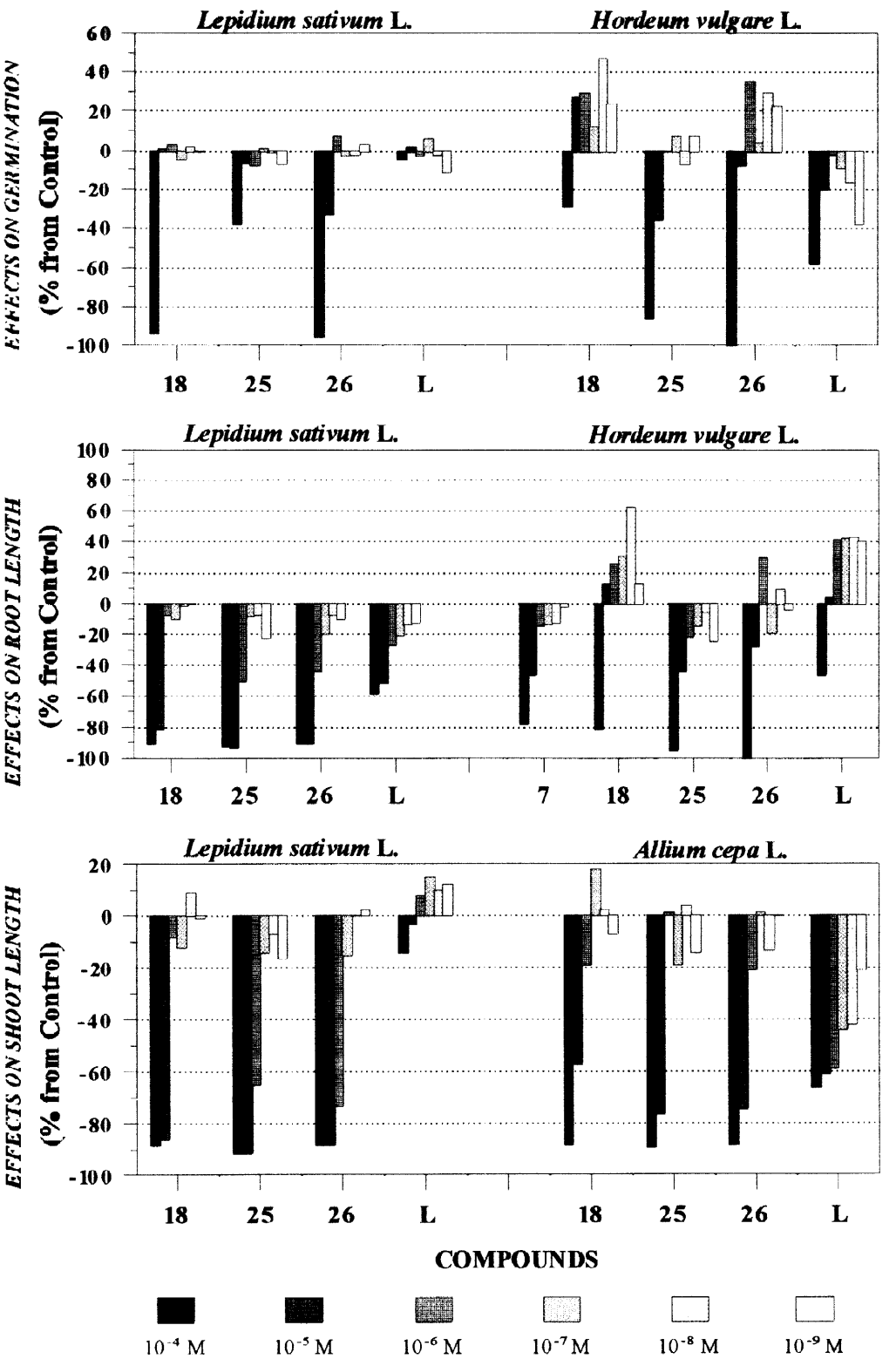
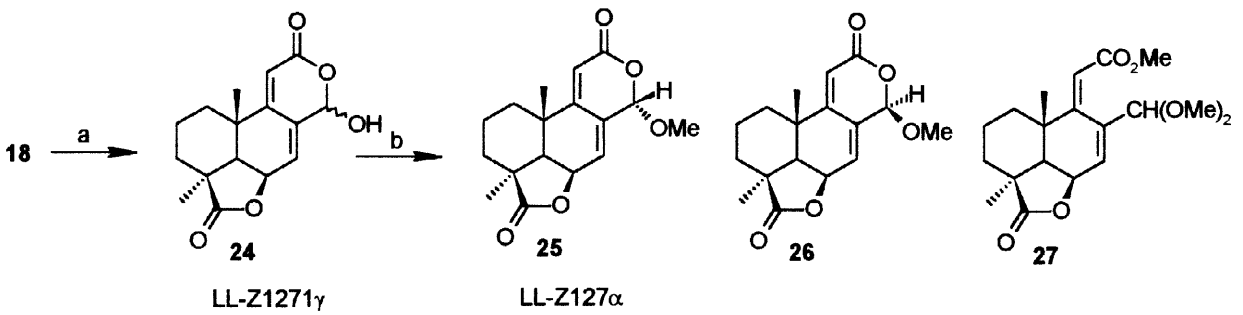


Figure 2. Effects of selected allelopathic compounds **7**, **18**, **25** and **26** in the germination, radical and shoot length of *L. sativum* L., *Allium cepa* L. and *H. vulgare* L. in comparison with the combination product terbutryn + triasulfuron (LOGRAN®, pre- and post-herbicide).

Z1271γ (isolated together with **25** from a species of *Acrostalagmus*) [2]. The antibiotic LL-Z1271α (**25**) was obtained (50%) together with its C-14 epimer (**26**) (35%) and the dimethylacetal **27** (15%) by treating **24** with methanol acidified with a drop of sulfuric acid [10].

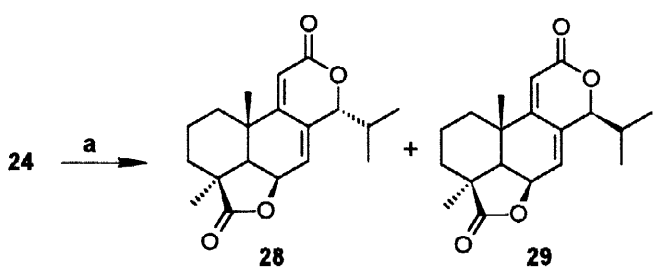
Scheme 7



(a) SeO_2, dioxane, 85%; (b) CH_3OH, H_2SO_4, 50% for **25**, 35% for **26**, 15% for **27**.

Treatment of the δ-hydroxylactone **24** with isopropylmagnesium bromide at 0 °C (Scheme 8) yielded 83% of condensation products, the main part (90%) of which was the α isomer nagilactone F (**28**), confirming the high stereoselectivity of the process. Under these conditions the magnesium compound does not attack the lactonic carbonyl groups. **28** is the most biologically active member of the dilactone family in the Yoshida sarcoma test [1].

Scheme 8



(a) i-PrMgBr, THF, 83%.

In order to evaluate the potential allelopathic activity of this podolactone series, we have studied the effect of a series of aqueous solutions at 10^{-4}-10^{-9} M of selected synthetic compounds on root and shoot length from two dicotyledon species (*Lactuca sativa* and *Lepidium sativum*) and two monocotyledon species (*Allium cepa* and *Hordeum vulgare)* as common standard target species (STS) for allelopathic studies [16].

The most relevant effect observed is the general strong inhibition of germination and growth development produced by **18**, **25** and **26** (average -90%) at 10^{-4} M concentration over all tested species, as previously reported for other members of these series [17]. A selection of the best results are shown in Figure 2. It is also important to notice the stimulation effect shown by **18** with dilution (average 35%) over germination and growth of monocotyledon species.

A common structural requirement of compounds **18**, **25** and **26**, the presence of a γ-lactone group between C-19 and C-6, could be related to these activities. The presence of the lactonic group may fix a preferent conformation for those molecules and consequently the activity can be related to the accessibility of the 7,9-dien-12,14-δ–lactone system. On the other hand, the presence of a methoxy group in C-14 enhances the inhibitory activity (**25**, **26**, -50%, about 10^{-6}M).

A comparison of the more active compounds with the commercial herbicide LOGRAN® (**L** in Figure 2) showed, in general, a better profile of activities particularly for concentrations of 10^{-4}M and 10^{-5}M in all the seeds tested. These findings suggest that compounds **18, 25 and 26** are good candidates for potential herbicide templates with potential use as a new generation of natural agrochemicals and in the case of **18** with application on monocotyledon crops when concentrations below 10^{-4}M are used.

3. Experimental

General experimental procedures

Optical rotations were determined on a Perkin-Elmer 141 polarimeter. IR spectra were obtained, in liquid film between NaCl plates, on a 983 G Perkin-Elmer apparatus. HRMS were measured on an Autospec-Q VG-Analytical (FISONS) mass spectrometer and LRMS were determined on a 5988A Hewlett-Packard instrument. NMR spectra were recorded on Bruker AM 300 and Bruker ARX 400 spectrometers. Chemical shifts are reported in parts per million (δ) relative to TMS and coupling constants (J) are in Hertz. ^{13}C NMR assignments are tentative unless otherwise stated. Melting points were determined on a Electrotermal Melting Point apparatus. Thin-layer chromatography (TLC) was performed on precoated 0.25-mm thick Merck plates of Si gel 60 F_{254}, using a 7% phosphomolybdic acid solution (EtOH) to visualize the spots. Gravity column chromatography was carried out on Merck silica gel 60 (70-230 mesh) and flash chromatography on Merck silica gel 60 (230-400 mesh).

Formation of aldehyde 3

An aqueous solution (10 mL) of 0.5 M sodium bicarbonate was added to a stirred solution of **1** (1 g, 3.16 mmol) in dichloromethane (50 mL). The resulting mixture was cooled to -10 °C and then a solution of *m*-chloroperbenzoic acid (0.81 g, 4 mmol) in dichloromethane (16 mL) was added dropwise over 30 min. The reaction mixture was stirred for 5 h at -10 °C. Then it was warmed to 0 °C for 3 h. After dilution with ether, sequential washing with 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride, drying over Na_2SO_4, removal of the solvent and column chromatography (20% *t*-BuOMe/hexane), an 8:5 mixture of **2α**, **2β** (0.88 g, 84%) was obtained [11]. Periodic acid (0.69 g, 3.01 mmol) was added to the mixture **2** (1 g, 3.01 mmol) in dry THF (50 mL). The reaction was stirred for 0.5 h at room temperature and then quenched with 50 mL of water. The THF was removed and the aqueous layer was extracted with ether. The organic layers were dried (Na_2SO_4), vacuum concentrated and chromatographed (20% *t*-BuOMe/hexane) to give **3** (0.728 g, 87%) [10].

Oxidation of 3 and esterification

Jones reagent (2.67 M solution, 7.0 mL, 11.7 mmol) was added to a solution of **3** (2 g, 7.2 mmol) in acetone (30 mL) and the mixture was stirred for 30 min at 0 °C. The reaction product was diluted with water and extracted with ether to give a substance which was esterified with CH_2N_2 in ether, yielding **4** (2 g, 90%) [18] as a white solid, m.p. 109-110 °C; $[\alpha]_D^{20}$ +16.3 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3020, 2950, 2850, 1735, 1720, 1645, 1440, 1225, 1160 cm^{-1}; δ_H (80 MHz, $CDCl_3$) 4.75 (1 H, br s, H-17), 4.46 (1 H, br s, H'-17), 3.62 (3 H, s, OMe), 3.60 (3 H, s,

OMe), 2.40 (2 H, s, H-11), 1.19 (3 H, s, H-18), 0.53 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 177.6, 174.2, 148.65, 106.37, 56.0, 51.9, 51.6, 51.2, 44.3, 39.6, 39.1, 38.2, 38.0, 30.9, 28.8, 25.8, 19.9, 12.7; *m/z* (EI) 308 (5, M^+), 277 (5), 248 (35), 217 (7), 201 (7), 180 (12), 175 (10), 161 (10), 121 (100); HRMS (EI): M^+, found 308.1988. $C_{18}H_{28}O_4$ requires 308.1973.

Epoxidation of ***4***

A solution of *m*-chloroperbenzoic acid (0.9 g, 4.45 mmol) in dichloromethane (20 mL) was added dropwise to a stirred solution of **4** (1.0 g, 3.25 mmol) in dichloromethane (50 mL) at 0 °C over 30 min. The reaction mixture was stirred for 2 h at the same temperature, then warmed to room temperature for 5 h, whereupon the organic phase was diluted with ether, washed sequentially with 5% aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over sodium sulphate and evaporated. Column chromatography (20% *t*-BuOMe/hexane) of the resulting white oil gave **11** (890 mg, 85%) and **12** (155 mg, 15%). **11**: colourless solid, m.p. 104-105 °C; $[\alpha]_D^{20}$ –2.1 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2950, 1721, 1435, 1370, 1306, 1226, 1156, 1093 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.62 (6 H, s, OMe), 2.62 (1 H, dd, *J* 4.1, 1.5 Hz, H-14), 2.51 (1 H, br d, *J* 4.1 Hz, H'-14), 2.29 (1 H, dd, *J* 7.2, 5.4 Hz, H-9), 2.16 (1 H, br d, *J* 13.5 Hz, H-3β), 2.07 (1 H, dd, *J* 16.0, 5.4 Hz, H-11), 1.88 (1 H, dd, *J* 16.0, 7.2 Hz, H'-11), 1.78 (1 H, ddddd, *J* 14.2, 13.6, 13.5, 3.5, 3.4 Hz, H-2β), 1.50 (1 H, br d, *J* 13.5 Hz, H-1β), 1.47 (1 H, br d, *J* 14.2 Hz, H-2α), 1.40 (1 H, br d, *J* 11.4 Hz, H-7), 1.33 (1 H, dd, *J* 11.7, 3.0 Hz, H-5), 1.20 (3 H, s, H-18), 1.16 (1 H, ddd, *J* 13.6, 13.5, 4.3 Hz, H-1α), 1.04 (1 H, ddd, *J* 13.6, 13.5, 4.0 Hz, H-3α), 0.63 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 177.6, 174.1, 58.5, 55.4, 51.8, 51.4, 50.2, 49.4, 44.2, 39.8, 38.9, 38.0, 36.2, 28.9, 27.6, 23.3, 19.4, 13.0; *m/z* (EI) 324 (1, M^+), 306 (1), 293 (4), 264 (15), 237 (100), 163 (12), 147 (12), 123 (16), 121 (21), 109 (36); HRMS (EI): M^+, found 324.1937. $C_{18}H_{28}O_5$ requires 324.1930. **12**: colourless oil; $[\alpha]_D^{20}$ +16.9 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2950, 1721, 1435, 1370, 1306, 1226, 1156, 1093 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.66 (3 H, s, OMe), 3.64 (3 H, s, OMe), 2.42 (1 H, d, *J* 3.6 Hz, H-14), 2.33 (1 H, d, *J* 3.6 Hz, H'-14), 2.20 (1 H, br d, *J* 13.5 Hz, H-3β), 1.83 (1 H, ddddd, *J* 14.2, 14.0, 13.5, 3.6, 3.6 Hz, H-2β), 1.70 (1 H, br d, *J* 13.0 Hz, H-1β), 1.49 (1 H, br d, *J* 14.2 Hz, H-2α), 1.37 (1 H, br d, *J* 12 Hz, H-7), 1.34 (1 H, dd, *J* 12.4, 2.6 Hz, H-5), 1.21 (3 H, s, H-18), 1.10 (1 H, ddd, *J* 14.0, 13.0, 4.0 Hz, H-1α), 1.06 (1 H, ddd, *J* 13.5, 13.5, 4.1 Hz, H-3α), 0.69 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 177.7, 174.8, 57.7, 55.5, 51.9, 51.4, 49.2, 47.2, 44.2, 39.5, 39.2, 38.1, 35.6, 28.7, 27.4, 21.6, 19.2, 13.2; *m/z* (EI) 324 (1, M^+), 306 (2), 293 (8), 292 (11), 264 (15), 247 (12), 237 (74), 182 (36), 173 (21), 161 (27), 143 (37), 135 (36), 123 (100), 109 (57); HRMS (EI): M^+, found 324.1937. $C_{18}H_{28}O_5$ requires 324.1930.

Opening of the epoxide ***11*** *with* $Al(OiPr)_3$

$Al(OiPr)_3$ (70 mg) was added to a stirred solution of the epoxy diester **11** (0.105 g, 0.326 mmol) in toluene (8 mL). The mixture was heated under reflux for 2 h. The reaction was monitored by TLC. After cooling, the mixture was washed twice with water, dried (Na_2SO_4), and the solvent removed to give a crystalline residue, which was purified by column chromatography (40% *t*-BuOMe/hexane), yielding **13** (68 mg, 71%), **14** (5 mg, 5%) and **15** (11 mg, 11%). **13**: white solid, m.p. 98-100 °C; $[\alpha]_D^{20}$ –11.4 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2953, 1717, 1466, 1448, 1412, 1375, 1356, 1333, 1222, 1193, 1177, 1152, 1096, 1073, 1037 cm^{-1}; δ_H (300 MHz, $CDCl_3$)

4.39 (1 H, dd, *J* 13.1, 11.7 Hz, H-14), 4.26 (1 H, dd, *J* 11.7, 7.2 Hz, H'-14), 3.61 (3 H, s, OMe), 2.61 (1 H, br d, *J* 18.3 Hz, H-11), 2.40 (1 H, dd, *J* 18.3, 7.7 Hz, H'-11), 2.26 (1 H, m, H-8), 2.17 (1 H, br d, *J* 13.3 Hz, H-3β), 1.44 (1 H, br d, *J* 14.3 Hz, H-2α), 1.16 (3 H, s, H-18), 1.13 (1 H, dd, *J* 8.7, 6.3 Hz, H-5), 1.01 (1 H, ddd, *J* 13.4, 13.3, 4.2 Hz, H-3α), 0.90 (1 H, ddd, *J* 14.2, 12.9, 4.1 Hz, H-1α), 0.73 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 177.5, 171.1, 71.8, 55.7, 51.5, 45.3, 43.9, 40.0, 38.1, 38.0, 30.8, 30.8, 28.7, 27.4, 19.3, 18.8, 14.3; ^1H and ^{13}C NMR data were assigned on the basis of 2D NMR experiments: direct heteronuclear $^1H/^{13}C$ correlation (HETCOR); *m/z* 294 (12, M^+), 279 (1), 262 (15), 235 (30), 234 (34), 219 (6), 217 (7), 201 (11), 194 (85), 175 (12), 165 (11), 161 (10), 147 (12), 135 (54), 134 (46), 121 (65), 119 (32), 109 (50), 107 (49), 105 (32), 101 (16), 95 (68), 93 (63), 91 (52), 81 (80), 79 (75), 77 (40), 69 (34), 67 (78), 59 (43), 55 (100), 53 (53); HRMS (FAB): MNa^+, found 317.1729. $C_{17}H_{26}O_4Na$ requires 317.1729. **14**: colourless oil; $[\alpha]_D^{20}$ +38.1 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2935, 2874, 2852, 1718, 1463, 1432, 1259, 1236, 1199, 1145, 1039 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.70 (1 H, m, H-7), 4.67 (1 H, br d, *J* 13.4 Hz, H-14), 4.59 (1 H, ddd, *J* 13.4, 2.7, 1.5 Hz, H'-14), 3.65 (3 H, s, OMe), 2.70 (1 H, br dd, *J* 19.2, 11.8 Hz, H-6β), 2.58 (1 H, dd, *J* 19.2, 10.2 Hz, H-6α), 2.19 (1 H, dddd, *J* 13.5, 3.4, 3.2, 1.7 Hz, H-3β), 1.85 (1 H, ddddd, *J* 13.7, 13.7, 13.4, 3.4, 3.4 Hz, H-2β), 1.76 (1 H, br d, *J* 13.4 Hz, H-1β), 1.19 (3 H, s, H-18), 1.06 (1 H, ddd, *J* 13.4, 13.4, 3.8 Hz, H-1α), 1.04 (1 H, ddd, *J* 13.7, 13.5, 4.2 Hz, H-3α), 0.61 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 177.0, 174.0, 133.8, 123.4, 70.8, 51.6, 50.6, 46.1, 44.1, 38.3, 38.2, 35.5, 30.1, 28.43, 24.5, 19.4, 12.1; *m/z* (EI) 292 (2, M^+), 277 (1), 260 (7), 232 (53), 217 (5), 188 (4), 173 (7), 159 (12), 119 (11), 109 (100); HRMS (EI): M^+, found 292.1675. $C_{17}H_{24}O_4$ requires 292.1675. **15**: colourless solid, m.p. 123-125 °C; $[\alpha]_D^{20}$ +10.3 (*c* 0.4, $CHCl_3$); ν_{max} (film) 3450, 2946, 2851, 1763, 1720, 1463, 1380, 1332, 1299, 1235, 1198, 1147, 1093 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.04 (1 H, d, *J* 12.5 Hz, H-14), 4.02 (1 H, d, *J* 12.5 Hz, H'-14), 3.66 (3 H, s, OMe), 2.68 (1 H, dd, *J* 18.0, 13.0 Hz, H-11), 2.52 (1 H, dd, *J* 18.0, 6.2 Hz, H'-11), 1.22 (3 H, s, H-18), 0.83 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 178.3, 177.5, 86.9, 69.5, 52.4, 51.5, 49.8, 43.8, 41.2, 37.9, 36.3, 32.8, 30.1, 28.7, 19.0, 18.9, 14.1; *m/z* (EI) 310 (1, M^+), 309 (1), 295 (3), 279 (5), 263 (4), 248 (31), 233 (10), 219 (18), 173 (22), 141 (50), 121 (100), 109 (42); HRMS (FAB): MNa^+, found 333.1678. $C_{17}H_{26}O_5Na$ requires 333.1678.

*Opening of the epoxide **11** with PTSA under reflux*

PTSA (35 mg) was added to a stirred solution of the epoxy diester **11** (0.2 g, 0.62 mmol) in benzene (10 mL). The mixture was heated under reflux for 8 h. The reaction was monitored by TLC. After cooling, the mixture was washed twice with water, dried (Na_2SO_4), and the solvent removed to give a crystalline residue. This was purified by column chromatography (40% *t*-BuOMe/hexane) yielding **7** (135 mg, 75%) and **14** (14 mg, 8%).

*Opening of the epoxide **11** with PTSA at low temperature*

PTSA (35 mg) was added to a cooled solution of **11** (0.2 g, 0.62 mmol) in $CHCl_3$ at -10 °C. The mixture was stirred for 1 h. Then it was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent a 4:1 mixture of **15** and **15'** was obtained. **15'**: colourless oil; $[\alpha]_D^{20}$ +20.5 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 3450, 2946, 2848, 1763, 1717, 1463, 1270, 1234, 1198, 1146 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.64 (3 H, s, OMe), 3.51 (1 H, d, *J* 12.0 Hz, H-14), 3.49

(1 H, d, *J* 12.0 Hz, H'-14), 2.91 (1 H, dd, *J* 18.0, 8.4 Hz, H-11) , 2.34 (1 H, d, *J* 18.0 Hz, H'-11), 2.22 (1 H, dd, *J* 15.1, 1.3 Hz, H-7), 2.16 (1 H, dt, *J* 15.1, 4.0 Hz, H'-7), 2.02 (1 H, d, *J* 8.4 Hz, H-9), 1.22 (3 H, s, H-18), 0.74 (3 H, s, H-20); δ_C ($CDCl_3$, 75 MHz) 178.5, 177.5, 87.0, 69.2, 52.2, 51.4, 49.6, 43.7, 41.0, 37.8, 36.2, 32.7, 30.0, 28.6, 18.9, 18.8, 14.0; *m/z* (EI) 310 (5, M^+), 309 (52), 295 (25), 277 (13), 264 (10), 249 (10), 237 (25), 233 (25), 217 (16), 173 (27), 121 (100), 109 (53); HRMS (FAB): MNa^+, found 333.1678. $C_{17}H_{26}O_5Na$ requires 333.1678.

Synthesis of 7 via organomercurials

A solution of **4** (1 g, 3.25 mmol) and mercuric acetate (2.07 g, 6.5 mmol) in 40 mL of anhydrous toluene was heated under reflux for 1 h. The cooled solution was filtered and the solvent removed, yielding a mixture (8:1) of mercurials **5** and **6** [9]. This mixture was dissolved in 34 mL of anhydrous DMF and subjected to vigorous oxygenation whilst a solution of 180 mg of $NaBH_4$ in 20 mL of DMF was added over 3 h. After a further 10 min of oxygenation 25 mL of H_2SO_4 (1N) were added. The mixture was extracted with ether, washed with a saturated $NaHCO_3$ solution and distilled water, dried over Na_2SO_4 and the solvent removed. The resulting substance was chromatographed (40% *t*-BuOMe/hexane) over silica gel, which yielded **7** (712 mg, 75%), **8** (140 mg, 15%) and **4** (50 mg, 5%). **7**: colourless solid, m.p. 108-110 °C; $[\alpha]_D^{20}$ +78.2 (*c* 0.8, $CHCl_3$); ν_{max} (neat) 2950, 2848, 1789, 1720, 1460, 1432, 1234, 1194, 1176, 1143, 1097 cm^{-1}; NMR data in reference [9]; *m/z* (EI) 292 (21, M^+), 264 (13), 260 (6), 233 (35), 232 (26), 217 (36), 199 (12), 189 (11), 173 (26), 171 (23), 161 (22), 159 (21), 145 (22), 119 (27), 107 (53), 91 (78), 59 (100); HRMS (EI): M^+, found 292.1677. $C_{17}H_{24}O_4$ requires 292.1675. **8**: white solid, m.p. 78-80 °C; $[\alpha]_D^{20}$ −71.1 (*c* 0.8, $CHCl_3$); ν_{max} (neat) 2942, 2874, 1717, 1662, 1457, 1380, 1232, 1195, 1169, 1141 cm^{-1}; NMR data in reference [9]; *m/z* (EI) 290 (9, M^+), 258 (18), 230 (43), 215 (17), 200 (100), 186 (47), 174 (58), 171 (56), 157 (36), 145 (44), 131 (38), 117 (29), 115 (38), 105 (31), 91 (51); HRMS (EI): M^+, found 290.1518. $C_{17}H_{22}O_4$ requires 290.1518.

Dehydrogenation of 7

DDQ (0.465 g, 2.054 mmol) and PTSA (0.353 g, 2.054 mmol) were added to a solution of **7** (0.3 g, 1.027 mmol) in dry dioxane (22 mL) The mixture was refluxed under nitrogen for 3 h, the solvent removed and the residue dissolved in sodium bicarbonate solution (30 mL) and extracted with ether, washed with brine, dried over anhydrous sodium sulphate and evaporated. After column chromatography (40% *t*-BuOMe/hexane), compounds **8** (150 mg, 50%), **9** (55 mg, 19%) and **10** (20 mg, 6%) were obtained. **9**: colourless oil; $[\alpha]_D^{20}$ +11.2 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2950, 2874, 1717, 1628, 1448, 1236, 1192, 1147 cm^{-1}; NMR data in reference [9]; *m/z* (EI) 290 (68, M^+), 262 (12), 247 (28), 231 (27), 217 (24), 215 (24), 202 (23), 187 (100), 171 (37), 159 (43), 145 (26), 131 (49), 119 (31), 105 (46), 91 (75); HRMS (EI): M^+, found 290.1513. $C_{17}H_{22}O_4$ requires 290.1518. **10**: yellow oil; $[\alpha]_D^{20}$ −5.7 (*c* 0.14, $CHCl_3$); ν_{max} (film) 2949, 2876, 1727, 1666, 1613, 1580, 1545 cm^{-1}; ^{1}H-NMR data in reference [9]; δ_C (75 MHz, $CDCl_3$) 176.8, 164.8, 163.1, 145.4, 130.0, 117.7, 115.0, 108.4, 51.7, 49.4, 43.4, 38.2, 36.9, 34.7, 27.0, 19.8, 19.0; *m/z* (EI) 288 (43, M^+), 228 (37), 213 (23), 200 (10), 185 (19), 173 (11), 161 (100), 145 (17), 141 (13), 132 (33), 128 (27), 115 (36); HRMS (FAB): MH^+, found 289.1438. $C_{17}H_{21}O_4$ requires 289.1440.

*Conversion of **9** to **7***

A solution of **9** (0.2 g, 0.69 mmol) in THF (7 mL), $NaBH_4$ (0.04 g) and 3M NaOH (3 mL) was refluxed for 3 h. After cooling, the resulting mixture was acidified with 2N HCl and extracted with ether. After washing with water, drying over anhydrous Na_2SO_4, filtering and column chromatography (40% *t*-BuOMe/hexane), 175 mg of **7** (87% yield) were obtained.

*Hydrolysis of **8** and treatment of **16** with the iodosobenzene diacetate-iodine system*

Dienolide ester **8** (0.1 g, 0.36 mmol) was dissolved in concentrated sulfuric acid (0.6 mL). After standing at room temperature for 24 h, the mixture was poured into ice and extracted with chloroform, affording **16** quantitatively as a colourless oil; $[\alpha]_D^{20}$ –95 (*c* 1.3, $CHCl_3$); ν_{max} (film) 2936, 1698, 1449, 1397, 1222, 1102, 1057, 1037, 923, 882, 755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.12 (1 H, m, H-7), 5.72 (1 H, br s, H-11), 4.86 (1 H, dddd, *J* 13.2, 3.7, 2, 2 Hz, H-14β), 4.77 (1 H, dddd, *J* 13.2, 2.2, 1.1, 1.1 Hz, H-14α), 2.93 (1 H, br dd, *J* 19.7, 11.7 Hz, H-6β), 2.56 (1 H, ddd, *J* 19.7, 5.7, 5.0 Hz, H-6α), 2.23 (1 H, ddd, *J* 13.5, 3.4, 3.2 Hz, H-3β), 1.65 (1 H, dd, *J* 11.7, 4.5 Hz, H-5), 1.46 (1 H, ddd, *J* 14.3, 13.7, 4.2 Hz, H-1α), 1.27 (3 H, s, H-18), 1.08 (1 H, ddd, *J* 13.5, 13.5, 4 Hz, H-3α), 1.00 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 182.6, 165.7, 162.9, 131.0, 125.3, 110.0, 69.7, 49.0, 44.1, 37.7, 37.6, 36.0, 28.4, 24.8, 19.4, 19.3; *m/z* (EI) 276 (100, M^+), 261 (10), 246 (11), 230 (71), 215 (33), 200 (62), 186 (30), 174 (55), 161 (40), 145 (32), 131 (35), 115 (41), 105 (49), 91 (79); HRMS (FAB): MNa^+, found 299.1260. $C_{16}H_{20}O_4Na$ requires 299.1259. A solution of **16** (130 mg, 0.47 mmol) in benzene-cyclohexane (1:1) (45 mL) containing iodosobenzene diacetate (167 mg, 0.52 mmol) and iodine (60 mg, 0.24 mmol) was irradiated with a 200W tungsten-filament lamp for 90 min at 35° C. The reaction mixture was then poured into water and extracted with ether. The organic layer was washed with aqueous sodium thiosulphate, water and dried over anhydrous Na_2SO_4. After removal of the solvent the residue was chromatographed (30% *t*-BuOMe/hexane), obtaining 46 mg of **17** (38% yield).**17a**: yellow oil; $[\alpha]_D^{20}$ –98.8 (*c* 0.08, $CHCl_3$); ν_{max} (film) 3413, 2962, 2926, 2878, 2855, 1707, 1653, 1559, 1540, 1456, 1394, 1254, 1197, 1101, 1051, 1018 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.06 (1 H, m, H-7), 5.75 (1 H, br s, H-11), 5.44 (1 H, m, H-3), 4.88 (2 H, m, H-14 and H'-14), 1.65 (3 H, br s, H-18), 1.00 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 162.5, 162.1, 132.5, 129.5, 126.0, 121.9, 109.6, 69.9, 45.0, 39.1, 35.4, 26.5, 22.3, 20.7, 17.4; HRMS (FAB): MNa^+, found 253.12065. $C_{15}H_{18}O_2Na$ requires 253.12045. **17b**: yellow oil; $[\alpha]_D^{20}$ 0 (*c* 0.42, $CHCl_3$); ν_{max} (film) 3418, 3082, 2932, 2858, 1717, 1647, 1598, 1450, 1396, 1377, 1257, 1219, 1199, 1174, 1095, 1051, 1021, 891 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.10 (1 H, m, H-7), 5.79 (1 H, d, *J* 1.8 Hz, H-11), 4.91 (2 H, m, H-14 and H'-14), 4.84 (1 H, d, *J* 1.4 Hz, H-18), 4.64 (1 H, d, *J* 1.4 Hz, H'-18), 0.93 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 165.5, 161.9, 147.9, 129.6, 126.7, 110.7, 108.6, 69.9, 42.4, 36.2, 35.9, 30.6, 25.7, 23.2, 18.5; HRMS (FAB): MNa^+, found 253.12045. $C_{15}H_{18}O_2Na$ requires 253.12045.

*Treatment of **16** with $Pb(AcO)_4$*

A mixture of **16** (530 mg, 1.92 mmol) and lead (IV) acetate (1516 mg, 3.42 mmol) in dry benzene (130 mL) was stirred at 10 °C for 62 h under irradiation with a 24 W fluorescent lamp. The reaction mixture was filtered, poured into water (50 mL) and extracted with ether. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and filtered. After removal

of the solvent a white oil (516 mg) was obtained. The residue was chromatographed (80% *t*-BuOMe/hexane) on silica gel to give the following compounds: **18** (265 mg, 50%), **17** (26 mg, 6%) and **19** (60 mg, 12%). **18**: white solid; ν_{max} (film) 2938, 2876, 1770, 1720, 1611 cm^{-1}; δ_C (75 MHz, $CDCl_3$) 180.9, 163.7, 158.8, 132.3, 121.8, 111.8, 71.3, 69.6, 47.9, 42.8, 35.1, 29.7, 24.8, 24.2, 17.4, 27.8; *m/z* (EI) 274 (24, M^+), 246 (100), 228 (27), 218 (23), 203 (30), 200 (34), 185 (27), 174 (40), 157 (21), 145 (49), 131 (31), 115 (31), 105 (16), 91 (35); HRMS (FAB): MNa^+, found 297.110379. $C_{16}H_{18}O_4Na$ requires 297.110279; all other data being consistent with previous reports [7]. **19**: colourless oil; $[\alpha]_D^{20}$ −71.5 (*c* 1.0, $CHCl_3$); ν_{max} (neat) 2929, 2871, 1717, 1455, 1377, 1254, 1218, 1200, 1127, 1096, 1043, 880 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.01 (1 H, m, H-7), 5.77 (1 H, d, *J* 1.8 Hz, H-11), 4.97 (1 H, d, *J* 14 Hz, H-14), 4.97 (1 H, m, H-6), 4.85 (1 H, d, *J* 14 Hz, H'-14), 2.36 (1 H, d, *J* 4.7 Hz, H-5), 1.46 (3 H, s, H-18), 1.41 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 164.0, 160.3, 131.1, 121.1, 111.1, 84.3, 74.4, 69.7, 59.2, 35.4, 30.2, 29.8, 27.4, 25.6, 17.6; *m/z* (EI) 262 (14, M^+), 247 (32), 244 (9), 219 (7), 201 (6), 177 (100), 149 (21), 121 (23), 91 (31); HRMS (FAB): MNa^+, found 285.110353. $C_{15}H_{18}O_4Na$ requires 285.110279.

*Preparation of **20***

A solution of dienolide **8** (0.5 g, 1.8 mmol) and SeO_2 (0.55 g, 5.4 mmol) in dioxane (30 mL) was refluxed for 1 h. After cooling, filtration and removal of the solvent, the residue was dissolved in 100 mL of ether and washed with water and brine. After drying and removal of the solvent, the residue was chromatographed (70% *t*-BuOMe/hexane) to give 475 mg of lactol **20** (90% yield) as a mixture (2:3) of C-14 α,β-epimers; ν_{max} (film) 3402, 2933, 2855, 1720, 1448, 1380, 1235, 1194, 1170, 1143, 1094, 1019, 979, 802, 755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.51 (1 H, m, H-7, α epimer), 6.33 (1 H, m, H-7, β epimer), 6.02 (1 H, br s, H-14, α epimer), 5.95 (1 H, br s, H-14, β epimer), 5.73 (1 H, br s, H-11), 5.48 (1 H, br s, OH, α epimer), 5.15 (1 H, br s, OH, β epimer), 3.67 (3 H, s, OMe), 3.04 (1 H, br dd, *J* 19.5, 11.5 Hz, H-6β, β epimer), 2.95 (1 H, br dd, *J* 19.5, 11.5 Hz, H-6β, α epimer), 2.58 (1 H, dt, *J* 19.5, 5.5 Hz, H-6α), 2.21 (1 H, br d, *J* 13.5 Hz, H-3β), 1.45 (1 H, ddd, *J* 13.5, 13.5, 4.2 Hz, H-1α), 1.20 (3 H, s, H-18), 1.05 (1 H, ddd, *J* 13.5, 13.5, 4 Hz, H-3α), 0.95 (3 H, s, H-20, β-epimer), 0.90 (3 H, s, H-20, α-epimer); δ_C (75 MHz, $CDCl_3$) β epimer: 176.5, 164.0, 160.0, 134.3, 127.6, 108.3, 95.3, 51.5, 48.0, 43.6, 37.0, 36.5, 35.2, 27.5, 24.4, 19.1, 18.2; δ_C (75 MHz, $CDCl_3$) α epimer: 176.5, 164.0, 160.9, 134.3, 128.1, 109.0, 95.0, 51.5, 48.2, 43.5, 36.8, 36.5, 35.4, 27.6, 24.4, 19.1, 18.2; HRMS (FAB): MNa^+, found 329.1363. $C_{17}H_{22}O_5Na$ requires 329.1365.

*Reaction of **20** with MeOH-H_2SO_4*

One drop of concentrated H_2SO_4 was added to 50 mg of the lactol **20** dissolved in 3 mL of absolute MeOH and the mixture was stirred for 2 h at room temperature. Then it was poured into ice and extracted with ether. The organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent, a mixture (55:45) of epimers **21** and **22** was obtained. **21**: ν_{max} (film) 3423, 2941, 2878, 2856, 1715, 1658, 1596, 1451, 1435, 1415, 1382, 1359, 1325, 1295, 1233, 1193, 1171, 1141, 1089, 1050 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.30 (1 H, m, H-7), 5.74 (1 H, br s, H-11), 5.47 (1 H, s, H-14), 3.68 (3 H, s, OMe), 3.52 (3 H, s, OMe), 3.04 (1 H, br dd, *J* 19.7, 11.5 Hz, H-6β), 2.40 (1 H, dt, *J* 19.7, 5.5 Hz, H-6α), 2.24 (1 H, br d, *J* 13.5 Hz, H-3β), 1.46 (1 H, ddd, *J* 13.5, 13.5, 4.2 Hz, H-1α), 1.22 (3 H, s, H-18), 1.07 (1 H, ddd, *J* 13.5, 13.5, 4

Hz, H-3α), 0.96 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 177.0, 164.2, 160.5, 135.7, 126.4, 108.8, 102.3, 56.0, 51.7, 48.9, 44.3, 37.7, 37.2, 35.9, 28.1, 25.1, 19.5, 18.7; *m/z* (EI) 320 (5, M^+), 305 (1), 289 (7), 288 (11), 261 (2), 260 (3), 245 (2), 229 (25), 216 (12), 201 (44), 200 (100), 185 (37), 173 (19), 161 (15), 145 (20), 131 (14), 129 (11), 128 (11), 115 (15), 105 (11), 91 (18), 77 (13), 59 (12), 55 (8), 53 85), 41 (14); HRMS (FAB): MNa^+, found 343.1521. $C_{18}H_{24}O_5Na$ requires 343.1521. **22**: ν_{max} (film) 3423, 2941, 2878, 2856, 1715, 1658, 1596, 1451, 1435, 1415, 1382, 1359, 1325, 1295, 1233, 1193, 1171, 1141, 1089, 1050 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.47 (1 H, m, H-7), 5.77 (1 H, br s, H-11), 5.69 (1 H, br s, H-14), 3.68 (3 H, s, OMe), 3.60 (3 H, s, OMe), 2.91 (1 H, br dd, *J* 19.7, 11.5 Hz, H-6β), 2.40 (1 H, dt, *J* 19.7, 5.5 Hz, H-6α), 2.24 (1 H, br d, *J* 13.5 Hz, H-3β), 1.46 (1 H, ddd, *J* 13.5, 13.5, 4.2 Hz, H-1α), 1.22 (3 H, s, H-18), 1.07 (1 H, ddd, *J* 13.5, 13.5, 4 Hz, H-3α), 0.92 (3 H, s, H-20); δ_C (75 MHz, $CDCl_3$) 177.1, 164.2, 161.0, 136.6, 126.9, 109.4, 101.6, 56.4, 51.7, 49.1, 44.02, 37.9, 37.4, 36.0, 28.3, 25.0, 20.0, 19.4; *m/z* (EI) 320 (5, M^+), 305 (1), 289 (6), 288 (11), 261 (2), 260 (3), 245 (2), 229 (20), 216 (11), 201 (39), 200 (100), 185 (35), 173 (18), 161 (16), 145 (19), 131 (13), 129 (10), 128 (11), 115 (14), 105 (9), 91 (17), 77 (12), 59 (11), 55 (7), 53 (5), 41 (12); HRMS (FAB): MNa^+, found 343.1521. $C_{18}H_{24}O_5Na$ requires 343.1521.

*Reaction of **20** with i-PrMgBr*

A spatula tip of I_2, 48 mg of Mg and 3 mL of anhydrous THF were placed in a stirred flask under argon. Isopropyl bromide (0.19 mL) in 1 mL of anhydrous THF was added slowly. When all the Mg was dissolved, 260 mg (0.85 mmol) of **20** dissolved in 2 mL of anhydrous THF were added slowly at 0 °C. The mixture was left for 4 h at room temperature. Then it was brought to acid pH by adding a saturated NH_4Cl solution and extracted with ether. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and the solvent was removed. Purification of the crude product by column chromatography (40% *t*-BuOMe/hexane) gave compound **23** (206 mg, 73%) as a white solid, mp 141-143 °C; $[\alpha]_D^{20}$ +36.7 (*c* 1.0, $CHCl_3$); HRMS (EI): M^+, found 332.198547. $C_{20}H_{28}O_4$ requires 332.198760; all other data being consistent with previous reports [4].

*Obtaining LL-Z1271γ (**24**)*

A solution of **18** (0.2 g, 0.73 mmol) and SeO_2 (0.3 g, 2.92 mmol) in dioxane (15 mL) was refluxed for 2 h. After cooling, filtration and removal of the solvent, the residue was dissolved in 50 mL of $CHCl_3$ and poured into water (100 mL). The aqueous layer was extracted with $CHCl_3$ and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and removal of the solvent, the residual oil was chromatographed (10% $CHCl_3$/*t*-BuOMe) on silica gel to yield 178 mg (85%) of the lactol **24**, which was not distinguishable from natural LL-Z1271γ in all respects: white solid; δ_C (75 MHz, $CDCl_3$) β epimer: 181.4, 163.4, 157.0, 135.1, 125.1, 111.5, 96.1, 72.1, 48.4, 43.5, 35.4, 30.1, 28.5, 24.5, 24.2, 18.1; δ_C (75 MHz, $CDCl_3$) α epimer: 181.4, 164.7, 158.2, 136.0, 123.8, 112.5, 95.9, 72.1, 49.7, 43.5, 35.6, 30.4, 28.5, 24.7, 24.3, 18.1; *m/z* (EI) 290 (31, M^+), 272 (98), 262 (15), 244 (100), 229 (35), 216 (34), 201 (63), 188 (46), 173 (45), 161 (31), 145 (28), 128 (36), 115 (44); all other data being consistent with previous reports [2].

Obtaining LL-Z1271α (25)

A solution of **24** (0.1 g, 0.34 mmol) in absolute MeOH (3 mL) was treated with one drop of concentrated H_2SO_4. The solution was stirred at room temperature for 2.5 h. The mixture was poured onto ice and extracted with $CHCl_3$. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed. The residual oil was chromatographed (80% *t*-BuOMe/hexane) on silica gel to afford of **25** (51 mg, 50%), **26** (36 mg, 35%) and **27** (18 mg, 15%). **25** was not distinguishable from natural LL-Z1271α in all respects: white solid, m.p. 214-215 °C; δ_C (75 MHz, $CDCl_3$) 180.8, 162.7, 157.5, 133.0, 124.1, 111.9, 101.2, 71.4, 57.5, 48.1, 42.8, 35.1, 30.0, 27.8, 24.7, 24.3, 17.5; *m/z* (EI) 304 (27, M^+), 289 (17), 276 (98), 272 (53), 262 (93), 245 (100), 231 (44), 217 (63), 201 (74); all other data being consistent with previous reports [2]. **26**: white solid; δ_C (75 MHz, $CDCl_3$) 180.8, 162.6, 156.4, 133.0, 125.2, 111.0, 101.9, 71.3, 56.6, 48.2, 42.8, 34.9, 29.7, 27.8, 24.3, 24.2, 17.4; all other data being consistent with previous reports [7]. **27**: colourless oil; NMR data in reference [9]; *m/z* (EI) 350 (26, M^+), 335 (8), 319 (71), 303 (8), 291 (10), 276 (63), 259 (20), 247 (75), 231 (29), 219 (18), 171 (15), 91 (11).

Preparation of Nagilactone F (28)

A spatula tip of I_2, 20 mg of Mg and 2 mL of anhydrous THF were placed into a stirred flask under argon. Isopropyl bromide (0.09 mL) in 1 mL of anhydrous THF was added slowly. When all the Mg was dissolved, 100 mg of **24** dissolved in 2 mL of anhydrous THF were added slowly at 0 °C. The mixture was left for 4 h at room temperature. Then it was brought to acid pH by adding a saturated NH_4Cl solution and extracted with ether. The organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of the solvent, a mixture 9:1 (90 mg, 83%) of **28** and **29** respectively was recovered. **28** was not distinguishable from natural nagilactone F in all respects: white solid, m.p. 224-226 °C; $[\alpha]_D^{25}$ -115 (*c* 0.2, MeOH); all other data being consistent with previous reports [19].

Lettuce, cress, onion and barley seed germination bioassay.

Lettuce seeds, L. saliva var. nigra and *Ho. vulgare*, were obtained from Rancho La Merced, Junta de Andalucía, Jerez, Spain. Seeds of *Lepidium sativum* and *Allium cepa* were obtained from Fitó S.L. All undersized and damaged seeds were discarded and the assay seeds were selected for uniformity of size.

Bioassay consisted of germinating 25 seeds for 5 days (3 for germination and 2 for root and shoot growth) for lettuce and onions, 3 days (1 for germination and 2 for root and shoot growth) for cress and 5 barley seeds, 4 days in the dark at 25 °C in 9 cm plastic Petri dishes containing a 10 cm sheet of Whatman No. I filter paper and 10 mL of a test of control solution, except for barley (5 mL). Test solutions (10^{-4} M) were prepared as the initial solution. Test solutions (10^{-5} -10^{-9} M) were obtained by diluting the previous solution. Parallel controls consisted of deionized H_2O.

There were 3 replicates for each treatment, except for barley (19 replicates) and parallel controls. The number of seeds per replicate, time and temperature for germination were chosen according to a number of preliminary experiments, with the number of seeds, volume of test

solution per dish and the incubation period all varying. All the pH values were adjusted to 6.0 before the bioassay using MES (2-[N-Morpholino]ethanesulfonic acid, 10 mM).

Statistical treatment. The germination, root and shoot length values were tested with the Mann-Whitney test, with the differences between the experiment and the control being significant with a value of $P = 0.01$.

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