First Synthesis of the Antifungal Oidiolactone C from *trans*-Communic Acid: Cytotoxic and Antimicrobial Activity in Podolactone-Related Compounds

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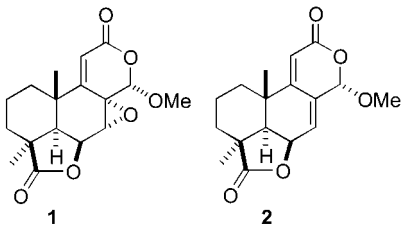
Received October 10, 2001

The synthesis of the fungicide oidiolactone C starting from diterpenic *trans*-communic acid was carried out with an overall yield of 11.7%. The key step in the process consists of a new bislactonization reaction catalyzed by Pd(II), which gives rise to the podolactone-type tetracyclic skeleton from a norlabdadienedioic acid. We also carried out a study of the structure−biological activity of different natural podolactones and their synthetic precursors. Thus, the highest cytotoxic activity was found in dienic dilactones with ether-type substitutions on C-17, whereas the closure of the γ-lactone ring is not critical for presenting a maximal antimicrobial activity.

Introduction

Podolactones are nor- or bisnorditerpenic compounds isolated mainly from different plants of the genus *Podocarpus* (family *Podocarpaceae*);[1] a number of dilactones isolated from filamentous fungi (*Oidiodendrum truncatum*,[2] *Aspergillus wentii*,[3] and *Acrostalamus* sp.[4]) have also been considered as part of this group. These molecules present a wide range of biological activities: antitumor,[5] insecticidal,[6] antifeedant,[7] allelopathic,[8] and fungicidal activities[9] deserving special attention. In relation to this antifungal activity, PR-1388 (**1**), LL-Z1271α (**2**), and oidiolactone C (**3**) were assayed against 11



strains of pathogenic yeasts, showing promising results against *Candida albicans* and other related species. Also worth mentioning are the results obtained against the dimorphic fungus *Histoplasma capsulatum*, which causes one of the most severe mycoses.[9] Recently, a patent appeared describing the production of terpenoid lactones from *Oidiodendrum griseum*,[10] an invention which also provides a pharmaceutical compound, comprising terpenoid lactones, useful in the treatment of IL-1 (interleukin-1) and TNF (tumor necrosis factor) mediated diseases.

Our group's interest in this class of compound led to a first synthetic procedure starting from a mixture of *trans*- and *cis*-communic acids (**4** and **5**) obtained from the cones of *Juniperus communis*.[11] The main drawback of this first method lies in the mixture of three isomers called "communic acids" (**4**−**6**), which required a chromatographic separation over silica gel impregnated with 20% silver nitrate to eliminate *mirceo*-communic acid (**6**) to allow use of the two-component mixture of cis- and trans-isomers as starting material. Furthermore, some steps in this former synthetic strategy, such as the closure of the δ-lactone or the formation of the dienolide system, needed improvement. With the aim of both continuing our studies on the possible use of these compounds as herbicides and also furthering our knowledge of the structure−cytotoxic relationship and antimicrobial activ-

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10.1021/jo0161882 CCC: $22.00
Published on Web 03/16/2002

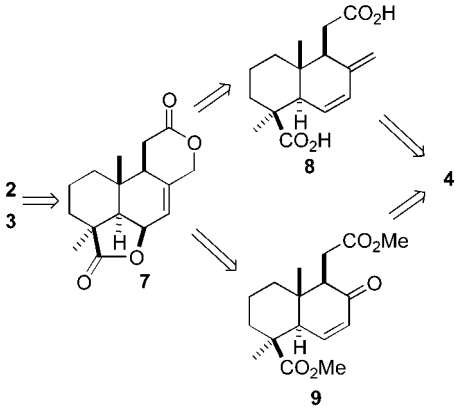


Figure 1. Retrosynthetic analysis for podolactones.

Table 1. Distribution of Communic Acids in the Cones of Some Conifers

species	wt %	relative proportion (*cis:trans:mirceo*)
J. communis L.	57	35:15:50
J. thurifera L.	3.7	6:3:1
J. phoenicea L.	3.3	1:1:0
C. sempervirens	2.3	0:1:0

ity, we communicate in this article the results concerning new and more efficient syntheses of podolactones, including those of the recently reported metabolite oidiolactone C, using only *trans*-communic acid (**4**) as starting material. We also report the results obtained from a comparative study on the cytotoxic and antimicrobial activity shown by different intermediates and final products.

Results and Discussion

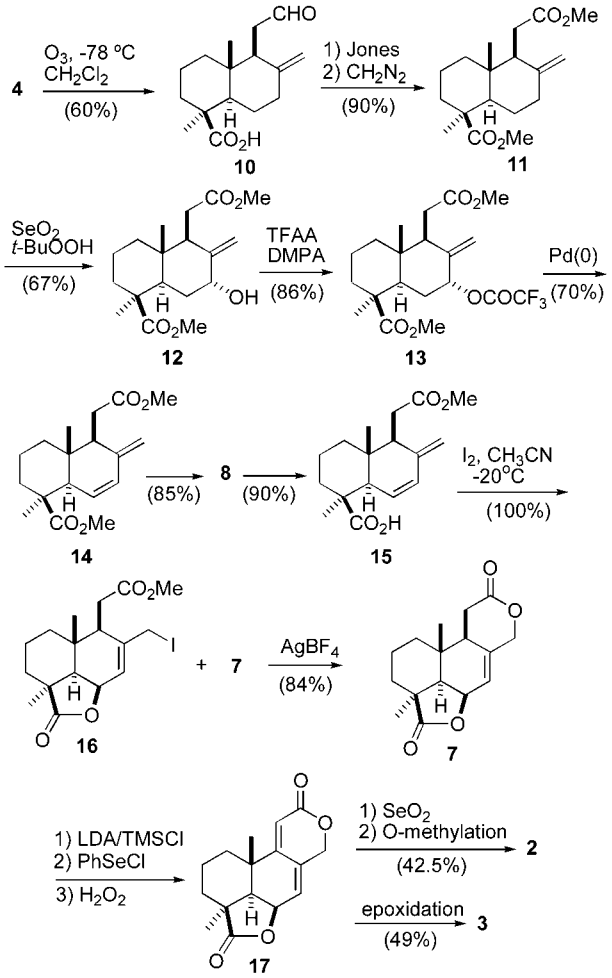
The preparation of bioactive podolactones such as oidiolactone C (**3**) or LL-Z1271α (**2**) was retrosynthetically planned as indicated in Figure 1, the starting material being *trans*-communic acid (**4**). Access to the final products would be achieved via dilactone **7** after introducing Δ^{9-11} and the appropriate functionalizations. The γ-lactone ring closure was envisioned to occur through the key intermediates **8** and **9**, both possessing the Δ^6 double bond, which could be obtained respectively by selective degradation of the side chain of **4** or by double degradation of the chain and the exocyclic double bond $\Delta^{8-(17)}$.

With regard to the election of the natural source of the starting material, we have studied the content in communic acids of the cones of *J. communis* in comparison with those of *Juniperus thurifera*, *Juniperus phoenicea*, and *Cupressus sempervirens* (Mediterranean cypress), the latter being quite abundant in Southern Spain (Table 1). The presence of only *trans*-communic acid (**4**) in the cones of cypress, easily isolated from the acid fraction on the hexane extract by crystallization of its sodium salt, was a determining factor for the selection of these cones.

The first synthetic approach to the total syntheses of the target molecules is summarized in Scheme 1 using diene **8** as key intermediate.

The selective degradation of **4** to **10** in 60% yield was realized via ozonolysis at low temperature; the compound resulting from the double degradation, keto aldehyde **18**, was obtained in 10% yield, and 10% of starting material was recovered. Starting material can be easily isolated and recycled from crude reaction, making this procedure

Scheme 1



noticeably more efficient than the previously reported ozonolysis of the corresponding methyl ester.[12]

Oxidation of aldehyde **10** and double esterification with diazomethane led to diester **11** with 90% yield. The next step was to oxidize regioselectively the allylic position C7. The best yields for the hydroxy derivative **12** (67% yield based on 60% conversion) were obtained by using 0.5 mol of SeO_2 and 2.5 mol of *t*-BuOOH per mol of **11**.

The elimination reactions in different acid media on the 7-hydroxy derivative were unsuccessful. Attempts to accomplish the regioselective elimination by derivatization of this alcohol as an ester and subsequent treatment with organic bases did not work satisfactorily either, diene **14** being obtained only in low yields.

A more efficient allylic elimination was acomplished by using Pd(0) complexes on different ester derivatives.[13,14] When the corresponding acetate, mesylate, and carbonate were treated with $Pd(PPh_3)_4$, only starting material was recovered. Fortunately, exposure of trifluoroacetate **13** to $Pd(PPh_3)_4$ resulted in the formation of diene **14** in an acceptable yield (72% based on 70% conversion). In the next step of the synthetic sequence, saponification of diester **14** was accomplished after

(12) Barrero, A. F.; Sánchez, J. F.; Altarejos, J. *Tetrahedron Lett.* **1989**, *30*, 5515−5518.
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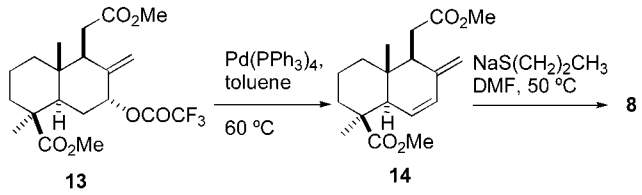
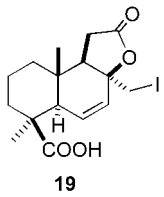
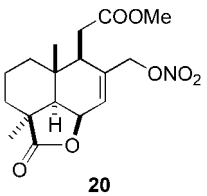
treating with sodium propanethiolate, diacid **8** being obtained in 85% yield.



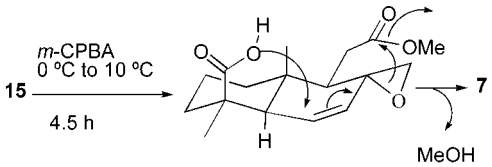
The application of the iodo lactonization method[15] to **8** following the conditions described by Barrett et al.[16] led regio- and stereoselectively to 12,8-γ-lactone **19** (96% yield). Then, with the aim of forcing the δ-lactone ring closure between C19 and C6, we proceeded to the selective protection of the carboxyl group at C12. The steric hindrance of the carboxyl group at C19 explains the selective formation of methyl monoester **15** (90% yield) when diacid **8** was treated with MeOH in the presence of 1,1′-carbonyldiimidazole. Iodo lactonization of **15** under Barrett's conditions after careful deoxygenation of the reaction medium furnished the iodo derivative **16** (80% yield) along with 20% of dilactone **7**.

Base-induced closure of the C12−C17 δ-lactone ring in **16** was unsuccessfully tried using $K_2CO_3/CH_3CN/H_2O$ and KOH/MeOH. To achieve this conversion, silver salt-catalyzed hydrolysis was envisioned.[17] In the event, exposure of **16** to $AgNO_3/H_2O$/acetone led to the desired **7** in 72% yield, along with alkyl nitrate **20** in 20% yield, whereas the use of $AgBF_4/H_2O$/acetone afforded exclusively dilactone **7** in 84% yield.



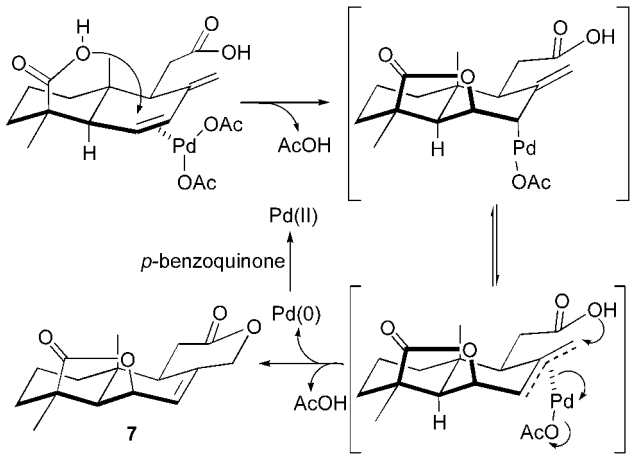


Two other new approaches to facilitate the formation of the desired dilactone were also pursued. In the first place, it was anticipated that dilactone **7** could conceivably be derived from monoester diacid **15** via a vinylogous epoxyde opening with concomitant ring closure and loss of methanol, in a process mechanistically related to the iodo lactonization. In the event, **7** was obtained directly in 70% yield when **15** was treated with 1.1 equiv of *m*-CPBA in CH_2Cl_2, the presence of the corresponding monoepoxide being noticed during the reaction process.



Alternatively, as a consequence of the close spatial relationship between both carboxyl groups in diacid **8** and the conjugated dienic system, the last approach to intermediate **7** was envisioned via 1,4-regioselective oxidation of conjugated dienes in the presence of Pd(II) complexes. Although this reaction has been described satisfactorily using catalytic amounts of Pd(II) with benzoquinone as a reoxidant and in the presence of protic acids,[18] only a few examples of intramolecular nucleophilic attack of a carboxylate leading to a monolactone have been described.[19] In our case, when diacid **8** was treated with substoichiometric Pd(II) (25%) and *p*-benzoquinone in a mixture of acetic acid and acetone as solvent, key intermediate **7** was obtained in 70% yield (based on 80% conversion).[20] This reaction constitutes the first example described of bislactonization of conjugated dienes. One possible pathway for this bis-cyclization is shown in Scheme 2.

Scheme 2



The requisite C9−C11 unsaturation was initially attempted via the selenylation/oxidation protocol. To find the best conditions for this conversion, diester **11** was used as a model. Direct conversion to phenylselenide **22** via the corresponding lithium enolate and subsequent addition of phenylselenenyl chloride was unsuccessful. After a good deal of careful experimentation, it was found that **22** could be obtained, via the corresponding silyl ketene acetal, when **11** was treated with 5 equiv of LDA and 7 equiv of TMSCl for 20 min and then with another 7 equiv of phenylselenenyl chloride. Application of the very same conditions to intermediate **7** led stereoselectively to 11α-phenylseleno lactone **24**. Oxidation of **24** to the corresponding selenoxide by hydrogen peroxide with concomitant syn elimination provided dienolide **17** in 80% overall yield. To complete the synthesis of oidiolactone C, **17** was treated with *m*-CPBA. Unfortunately, this reaction proceeded very slowly and only 5% of the target compound was obtained. Dimethyldioxirane was found to epoxidize **17** more efficiently, furnishing the desired dienolide **3** in 49% yield (based on 39% conversion). Synthetic **3** was found to display identical spectroscopic properties when compared to authentic oidiolactone C,[21] and an optical rotation value ($[\alpha]^{20}_D$ −12.0; c = 0.2, $CHCl_3$) confirmed the absolute configuration of the natural compound (Scheme 3). Previously, we had also reported the formation of **2** from **17**.[11]

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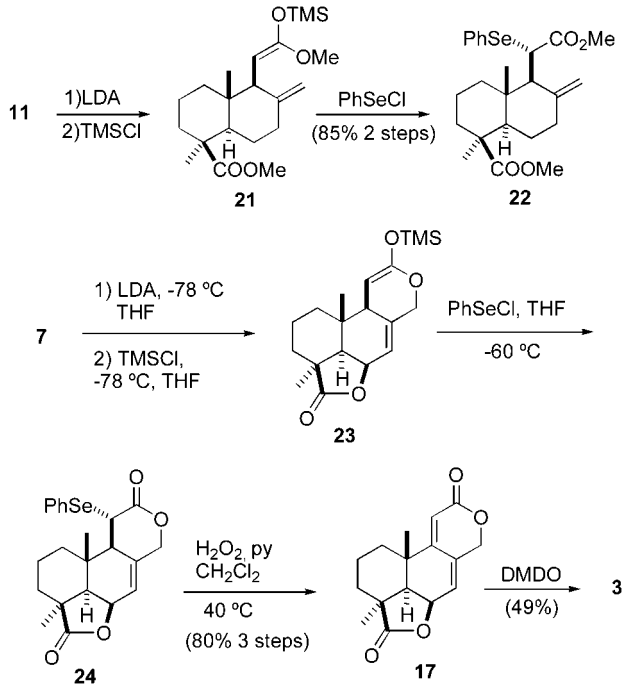
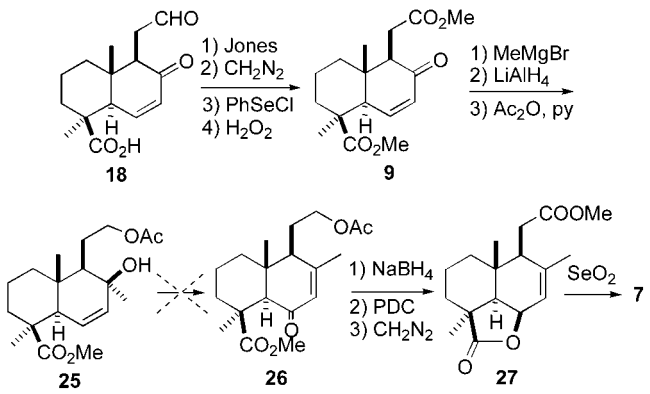
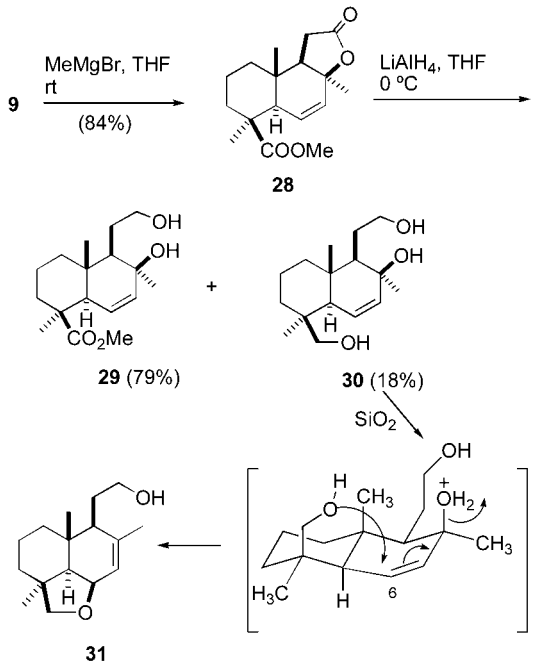
Scheme 3



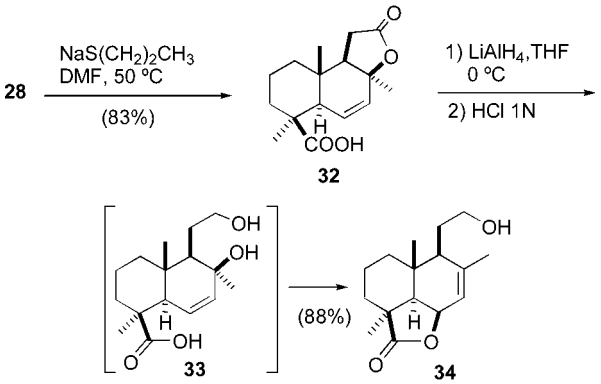
Scheme 4



Scheme 5



Scheme 6



Our initial proposal for the second synthetic strategy to oidiolactone C is shown in Scheme 4. This route commenced with the ozonolysis of *trans*-communic acid **4**. When this compound was exposed to ozone in excess, keto aldehyde **18** was obtained in 76% yield. Oxidation of **18** with Jones reagent and esterification with diazomethane, followed by treatment with PhSeCl in EtOAc and oxidation with H_2O_2, provided conjugated ketone **9** in 77% overall yield.

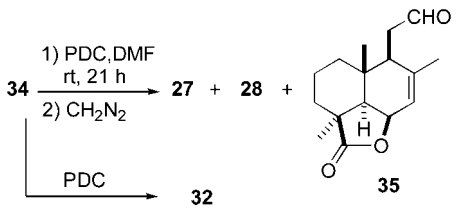
Addition of MeMgBr to **9** to introduce C17 of the podolactone skeleton was totally stereoselective and provided lactone **28** in 84% yield (based on 90% conversion). Chemoselective reduction of γ-lactone function with LAH at 0 °C afforded diol **29** in 79% yield, which was accompanied by reduction of the methyl ester to give triol **30** (18% yield). The latter compound was found to be acid-labile and underwent quantitative conversion to tetrahydrofuran derivative **31** via a S_N2' mechanism when subjected to chromatographic separation on silica gel (Scheme 5).

Acetylation of diol **29** under standard conditions gave rise to monoacetyl derivative **25**. Attempts to achieve allylic oxidation of **25** with PCC or PDC under the conditions described by Gao et al.[22] on similar substrates failed. To circumvent this problem, the proposed approach to key intermediate **27** was revised on the basis of the easy cyclization of triol **30**. Thus, there was good reason to believe that the desired γ-lactone closure could be accomplished via chemoselective reduction of the lactone moiety on compound **32**, which could be prepared by saponification of the methyl ester on **28** with sodium propanethiolate. Thus, exposure of the nonisolated intermediate **33** to the action of aqueous 1 N HCl at 0 °C led to the closure to the 6,19-lactone **34** in 88% overall yield (Scheme 6).

Oxidation of primary alcohol **34** with PDC in DMF furnished, after esterification with diazomethane, the corresponding methyl ester **27** with an acceptable yield (70%). Together with **27**, aldehyde **35** (8% yield) and lactone **28** (20% yield) were obtained. The latter resulted from the opposite cyclization to that described for the formation of **34** with concomitant opening of the 6,19-lactone. The completion of the synthesis of key lactone **7** only requires the allylic oxidation of the C-17 methyl with closure of the δ-lactone. This conversion was achieved with SeO_2 in refluxing acetic acid to yield **7** in 51% yield.

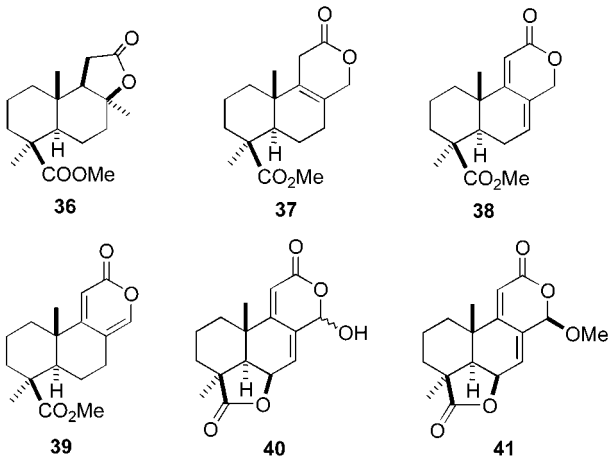
(22) Gao, W. G.; Sakaguchi, K.; Isoe, S.; Ohfune, Y. *Tetrahedron Lett.* **1996**, *37*, 7071−7074.

Scheme 7



After careful analysis of the results obtained from the two described approaches to oidiolactone C, it was noticed that an improvement to the synthesis could be achieved if intermediate **9** of the second route was homologated to diene **14** via the Wittig reaction or other methylenation reactions. This homologation was finally accomplished by treatment with the corresponding phosphorus ylide to yield diene **14** in 80% yield. Thus, the enantiospecific synthesis of oidiolactone C in 11 steps from **4** with 11.7% overall yield has been acomplished, improving noticeably the syntheses of podolactones described by Burke et al.[23] and by Adinolfi et al.[24]

In parallel with the chemical synthesis, we evaluated the antimicrobial activity of 18 molecules with podolactone-related structures, 12 of them prepared during this work and the rest obtained during our previous research.[11] These compounds were tested against selected Gram-positive and -negative bacteria and yeasts (Table 2) following a methodology described by our group.[25] Tested compounds were grouped on the basis of their structural similarities: group I, the bicyclic trinorlabdanes **9**, **11**, **13**, and **14**; group II, the tricyclic 12,8-olides **19**, **32**, and **36**; group III, the tricyclic 19,6-olides **27**, **34**, and **35**; group IV, the tricyclic 12,17-olides **37**−**39**; and group V, the tetracyclic 19,6:12,17-diolides **2**, **7**, **17**, **40**, and **41**. Previously reported data on the antifungal activity of oidiolactone C (**3**) (group V) are included in Table 2.[9]



An analysis of the results led to the following conclusions. Structural groups I−III lack activity. In group IV, maximum activity is shown by compound **38**, which was selective against Gram-positive bacteria and yeasts. In group V, three molecules (**2**, **17**, and **41**) show a relevant activity against yeasts and comparatively (from 4 to 8 times) less effect against Gram-positive bacteria. This comparison suggests certain structure−activity relationships. Thus, the presence of the 7,9(11)-dien-12,17-olide moiety is necessary to achieve the maximum activity against yeasts. For molecules possessing the abovementioned functionalities, the closure of the γ-lactone ring results in a remarkable lack of activity against Gram-positive bacteria

Assays of the antitumor activity in vitro have been achieved in some of the most representative compounds described in the article. Four cell lines, P-388 (mouse lymphome), A-549 (human lung carcinome), HT-29 (human colon carcinome), and MEL-28 (human melanome), were tested following established methods.[26] Results obtained are summarized in Table 3.

Conclusions

We have developed an efficient enantiospecific route toward oidiolactone C starting from easily available communic acids. The key step in this synthesis is the totally regio- and stereoselective palladium(II) bislactonization reaction, which is the first example described of bis-cyclization in this kind of oxidation. Although different synthetic routes to podolactones have been described in the literature, the approach described here is more efficient than the previous results. The study of the antimicrobial activity of different podolactones and synthetic precursors (some of them turned out to be remarkably active) permitted some structure−activity relationships to be established.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were measured at 300 or 400 MHz. ^{13}C NMR spectra were measured at 75 or 100 MHz. Microanalyses were recorded at the Servicios Técnicos (UGR). Chromatography was performed with flash-grade silica gel. All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an atmosphere of argon. Dry THF was obtained by distillation under argon from sodium−benzophenone ketyl. Methylene chloride, *N*,*N*-dimethylformamide (DMF), and diisopropylamine were distilled from calcium hydride. Dried cones were extracted as described elsewhere,[27] and their composition in communic acids was calculated after column chromatography of the decerated extract. *trans*-Communic acid (**4**) was isolated from *C. sempervirens* cones as follows: 2 kg of air-dried cypress cones were extracted with hexane in a Soxhlet apparatus, the resulting extract was defatted by precipitation at low temperature. The defatted extract (100 g) was dissolved in 300−400 mL of hexane and treated with 2 N NaOH to obtain 49.5 g of a white solid. This precipitate was composed mainly of **4** (2.3%).

Methyl 13,14,15,16-Tetranorlabd-8(17)-ene-12,19-dioate (11). A solution of **4** (3.0 g, 9.9 mmol) in 50 mL of CH_2Cl_2, cooled at −78 °C, was subjected to a stream of O_2/O_3 (30 nL/h) for 1.5 h. Then, argon was bubbled through for 10 min and 3 mL of dimethyl sulfide was added. The mixture was stirred for 6 h at room temperature and then concentrated under vacuum. Purification by column chromatography afforded alkene **10** (1725 mg, 66%),[12] ketone **18** (266 mg, 10%), and 300 mg of starting material (10%).

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Table 2. Antimicrobial Activity of Selected Compounds, MIC (μg/mL)[a]

		Gram-positive bacteria[b]			Gram-negative bacteria[c]			yeasts[d]		
		A	B	C	D	E	F	G	H	I
	9	>100	>100	>100	>100	>100	>100	>100		
group I	**11**	>100	>100	>100	>100	>100	>100	>100	>100	>100
	13	>100	>100	>100	>100	>100	>100	>100		
	14	>100	>100	>100	>100	>100	>100	>100		
	19	>100	>100	>100	>100	>100	>100	>100		
group II	**32**	>100	>100	>100	>100	>100	>100	>100		
	36	>100	>100	>100	>100	>100	>100	>100		
	27	>100	>100	>100	>100	>100	>100	>100		
group III	**34**	50−100	<50	50−100	>100	>100	>100	>100	>100	>100
	35	>100	>100	>100	>100	>100	>100	>100		
	37	25−50	25−50	25−50	>100	>100	>100	25−50	<25	<25
group IV	**38**	*<3.12*	*<3.12*	*<3.12*	50−100	50−100	50−100	*<6.25*	*<3.12*	*<6.25*
	39	12−25	50−100	50−100	>100	>100	>100	>100	25−50	>100
	2	>25	>25	>25	>100	>100	>100	*<3.12*	*<3.12*	*<3.12*
	7	>100	>100	>100	>100	>100	>100	>100		
group V	**17**	>25	>25	>25	>50	>50	>50	*<12.5*	*<6.25*	*<3.12*
	40	>25	>25	>25	>100	>100	>100	>25	>25	>25
	41	>25	>25	>25	>100	>100	>100	*<6.25*	*<6.25*	*<3.12*
	3							32		16

[a] The most promising results are in italic type. [b] A, *Enterococcus faecalis* S 48; B, *Bacillus subtilis* CECT 397; C, *Staphylococcus aureus ATCC 8.* [c] D, *Salmonella typhymurium* LT 2; E, *Escherichia coli*; F, *Proteus s.* [d] G, *Candida albicans* CECT 1394; H, *Saccharomyces cerevisiae*; I, *Cryptococum neoformans*.

Table 3. Cytotoxic Activity of Selected Compounds, IC_{50} (μg/mL)[a]

	P-388	A-549	HT-29	MEL-28
2	*0.12*	*0.12*	*0.25*	*0.25*
17	*0.5*	*0.5*	*1*	*1*
36	*2.5*	*5*	10	20
37	20	20	>20	>20
38	*2*	*2*	*5*	*2*
39	10	20	>20	>20
40	>10	>10	>10	>10
41	*0.1*	*0.1*	*0.12*	*0.12*

[a] The most promising results are in italic type.

Alkene **10** was oxidized and esterified as previously described[11] to give **11** (1800 mg, 90%).

Dimethyl 7α-Hydroxy-13,14,15,16-tetranorlabd-8(17)-ene-12,19-dioate (12). To an ice-chilled stirred suspension of SeO_2 (73 mg, 0.65 mmol) in CH_2Cl_2 (1 mL) was added *t*-BuOOH (5.5 M) in hexane (0.47 mL, 2.6 mmol). The mixture was stirred for 30 min and alkene **11** (400 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 2 h at 5−10 °C, the mixture was diluted and washed with water. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography using hexane: *t*-BuOMe to give 168 mg (40%; 66% based on recovered starting material) of **12** as a colorless oil: $[\alpha]^{20}_D$ −2.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.59 (s, 1H), 4.37 (br s, 1H), 3.63 (s, 3H), 3.61 (s, 3H), 2.90 (br d, J = 11.6 Hz, 1H), 2.51 (dd, J = 16.0, 4.0 Hz, 1H), 2.36 (dd, J = 16.0, 11.6 Hz, 1H), 2.15 (m, 2H), 2.04 (dd, J = 12.9, 2.9 Hz, 1H), 1.97 (br s, 1H), 1.79 (m, 1H), 1.62 (br d, J = 12.4 Hz, 1H), 1.53 (m, 1H), 1.25 (ddd, J = 13.2, 12.8, 3.2 Hz, 1H), 1.15 (s, 3H), 1.10 (ddd, J = 13.5, 13.5, 4.0 Hz, 1H), 0.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 174.1, 149.9, 108.9, 73.2, 51.6, 51.2, 48.1, 45.8, 43.8, 39.5, 38.7, 38.0, 31.9, 30.2, 28.5, 19.8, 11.7; IR (film) 3470, 3078, 2947, 1722, 1648 cm^{-1}; HRFABMS calcd for $C_{18}H_{28}O_5Na$ $[M + Na]^+$ 347.1834, found 347.1836.

Dimethyl 13,14,15,16-Tetranorlabda-6,8(17)-diene-12,-19-dioate (14). To a solution of 1000 mg (3.1 mmol) of **12** and 415 mg (3.4 mmol) of DMAP in 10 mL of CH_2Cl_2 was added dropwise 0.9 mL (6.2 mmol) of TFAA at 0 °C. After stirring 45 min at room temperature, the mixture was diluted with *t*-BuOMe and then cool water was added. The organic layer was separated, washed with 2 N HCl and brine, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography (hexane/*t*-BuOMe 4:1) to afford 1116 mg (86%) of trifluoroacetate **13** as a colorless solid: mp 99−101 °C; $[\alpha]^{20}_D$ −2.3 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (t, J = 3.0 Hz, 1H), 5.23 (br s, 1H), 4.87 (d, J = 1.7 Hz, 1H), 3.62 (s, 3H), 3.58 (s, 3H), 2.69 (br d, J = 11.1 Hz, 1H), 2.54 (dd, J = 15.9, 3.8 Hz, 1H), 2.33 (dd, J = 15.9, 11.2 Hz, 1H), 2.28 (br s, 1H), 2.26 (d, J = 3.0 Hz, 1H), 2.21 (br d, 13.5 Hz, 1H), 1.79 (m, 1H), 1.77 (br d, 1H), 1.63 (br d, J = 12.6 Hz, 1H), 1.55 (m, 1H), 1.26 (ddd, J = 13.2, 13.3, 4.1 Hz, 1H), 1.15 (s, 3H), 1.12 (ddd, J = 13.5, 13.5, 4.0 Hz, 1H), 0.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 173.1, 156.5 (q, $J(^{13}C,^{19}F)$ = 42 Hz), 142.9, 114.6 (q, $J(^{13}C,^{19}F)$ = 284 Hz), 114.3, 80.4, 51.8, 51.5, 49.4, 47.0, 43.8, 39.2, 38.5, 37.8, 30.5, 29.9, 28.5, 19.8, 12.0; IR (film) 1784, 1732, 1657, 874 cm^{-1}; HRFABMS calcd for $C_{20}H_{27}O_6F_3Na$ $[M + Na]^+$ 443.1657, found 443.1656. Anal. Calcd for $C_{20}H_{27}O_6F_3$: C, 57.14; H, 6.43. Found: C, 57.19; H, 6.79.

To a solution of 157 mg (0.37 mmol) of **13** in 2 mL of dry toluene was added 51 mg (0.37 mmol) of K_2CO_3 and 80 mg (0.074 mmol) of $Pd(PPh_3)_4$. The reaction mixture was heated at 60 °C for 6.5 h. Then, it was diluted with *t*-BuOMe and cool water was added. The organic layer was separated and washed with brine and concentrated. The residue was purified by column chromatography (hexane/*t*-BuOMe 85:15) to give 56 mg (50%, 72% based on recovered starting material) of **14** as colorless crystals: mp 82−84 °C; $[\alpha]^{20}_D$ −23.0 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (m, 2H), 4.86 (d, J = 1.6 Hz, 1H), 4.67 (br s, 1H), 3.67 (s, 3H), 3.58 (s, 3H), 2.68 (br d, J = 9.2 Hz, 1H), 2.53 (dd, J = 16.2, 3.4 Hz, 1H), 2.35 (dd, J = 16.2, 9.4 Hz, 1H), 2.26 (br s, 1H), 2.22 (br d, J = 13.4 Hz, 1H), 1.82 (qt, J = 13.7, 3.7 Hz, 1H), 1.58 (m, 2H), 1.27 (s, 3H), 1.19 (m, 1H), 1.07 (ddd, J = 13.5, 13.5, 4.2 Hz, 1H), 0.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 174.1, 145.2, 129.0, 128.0, 110.2, 55.2, 51.6, 51.1, 48.6, 43.3, 38.0, 37.0, 36.9, 30.8, 27.7, 19.5, 11.7; IR (film) 1740, 1719, 1637, 1597, 885, 698 cm^{-1}; HRFABMS calcd for $C_{18}H_{26}O_4Na$ $[M + Na]^+$ 329.1729, found 329.1730.

13,14,15,16-Tetranorlabda-6,8(17)-diene-12,19-dioic Acid (8). To a solution of **14** (160 mg, 0.53 mmol) in 9 mL of DMF was added 470 mg (4.8 mmol) of sodium propanothiolate. The reaction was stirred at 50 °C for 24 h. The mixture was recooled at 0 °C and diluted with *t*-BuOMe. Cool water was added, then the mixture was acidified to pH 2 with 2 N HCl and extracted with *t*-BuOMe. The combined extracts were dried over Na_2SO_4 and concentrated in a vacuum. Purification by flash chromatography (hexane/*t*-BuOMe 1:1) gave 125 mg (0.45 mmol, 85%) of **8** as white solid: mp 190 °C; $[\alpha]^{20}_D$ −10.0 (c = 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.18 (br d, J = 10.2 Hz, 1H), 6.08 (ddd, J = 10.2, 3.1, 3.1 Hz, 1H), 4.86 (br s, 1H), 4.76 (br s, 1H), 2.63 (br d, J = 9.2 Hz, 1H), 2.57

(ddd, J = 16.2, 3.2, 3.2 Hz, 1H), 2.31 (ddd, J = 16.1, 9.3, 3.5 Hz, 1H), 2.27 (br s, 1H), 2.19 (br d, J = 13.3 Hz, 1H), 1.90 (qq, J = 13.8, 3.7 Hz, 1H), 1.71 (m, 1H), 1.56 (m, 1H), 1.30 (s, 3H), 1.25 (m, 1H), 1.12 (ddd, J = 13.5, 13.5, 4.1 Hz, 1H), 0.62 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 180.5, 177.8, 147.2, 130.6, 129.1, 110.7, 56.2, 50.2, 44.3, 39.3, 38.3, 38.3, 32.0, 28.6, 20.8, 12.6; IR (film) 3300−2500 (wide band), 1700, 1643, 1600, 883, 691, 723 cm^{-1}; HRFABMS calcd for $C_{16}H_{20}O_4Na_3$ [M − 2H + 3Na]$^+$ 345.1055, found 345.1056.

13,14,15,16-Tetranorlabda-6,8(17)-diene-12,19-dioic Acid 12-Methyl Ester (15). To a solution of 400 mg (1.44 mmol) of diacid **8** in 8 mL of dry *t*-BuOMe were added 3.5 mL of dry MeOH, 800 mg (4.9 mmol) of carbonyldiimidazole, and 4 Å molecular sieves. The reaction was stirred at room temperature for 24 h. Then, the solvent was removed under vacuum and the residue diluted with water, acidified to pH 2 with 2 N HCl, and extracted with *t*-BuOMe. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (hexane/*t*-BuOMe 7:3) to afford 378 mg (90%) of **15** as white solid: mp 88−90 °C; $[\alpha]^{20}_D$ −16.7 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 2H), 4.87 (d, J = 1.8 Hz, 1H), 4.69 (br s, 1H), 3.68 (s, 3H), 2.68 (br d, J = 9.0 Hz, 1H), 2.53 (dd, J = 16.2, 3.4 Hz, 1H), 2.37 (dd, J = 16.2, 9.3 Hz, 1H), 2.28 (br s, 1H), 2.20 (br d, J = 13.6 Hz, 1H), 1.85 (qt, J = 13.7, 3.6 Hz, 1H), 1.60 (m, 2H), 1.33 (s, 3H), 1.08 (ddd, J = 13.6, 13.6, 4.2 Hz, 1H), 0.86 (m, 1H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 174.5, 145.3, 128.9, 128.6, 110.6, 55.3, 51.9, 48.8, 43.4, 38.4, 37.1, 37.0, 31.0, 28.1, 19.6, 12.1; IR (film) 3550−2500 (wide band), 1736, 1695, 1640, 1599, 886, 700 cm^{-1}; HRFABMS calcd for $C_{17}H_{24}O_4Na$ [M + Na]$^+$ 315.1572, found 315.1572.

Methyl 17-Iodo-13,14,15,16-tetranorlabd-7-en-19,6*β*-olide-12-oate (16). To a solution of I_2 (106 mg, 0.4 mmol) in dry deoxygenated acetonitrile (2 mL) was added at −20 °C dropwise a solution of monoacid **15** (40 mg, 0.14 mmol) in 4 mL of acetonitrile. The reaction mixture was stirred at −20 °C for 5 h. The mixture was then diluted with *t*-BuOMe, washed with saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford 60 mg of a crude mixture that showed the presence of dilactone **7** along with compound **16** in a 1:4 ratio. This mixture was not purified due to the instability of the allylic iodide. Compound **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (dd, J = 4.4, 2.5 Hz, 1H), 4.80 (m, 1H), 4.02 (d, J = 9.7 Hz, 1H), 3.95 (d, J = 9.7 Hz, 1H), 3.74 (s, 3H), 2.83 (m, 1H), 2.55 (dd, J = 16.4, 7.3 Hz, 1H), 2.41 (dd, J = 16.4, 4.5 Hz, 1H), 2.11 (m, 1H), 1.85 (d, J = 5.1 Hz, 1H-5), 1.71 (m, 1H), 1.53 (m, 2H), 1.34 (m, 2H), 1.33 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 173.7, 144.2, 123.5, 72.9, 52.4, 50.7, 46.2, 42.6, 34.1, 33.0, 30.9, 28.0, 24.1, 18.2, 18.0, 7.0; HRCIMS calcd for $C_{17}H_{24}O_4I$ [M + H]$^+$ 419.0719, found 419.0718.

13,14,15,16-Tetranorlabd-7-ene-(19,6*β*),(12,17)-diolide (7). Method A. The mixture **16** + **7** (29 mg ≈ 0.07 mmol, ratio 4:1) was dissolved in 1 mL of acetone and 2 mL of water. To this solution were added 0.05 mL (0.28 mmol) of collidine and 36 mg (0.21 mmol) of $AgNO_3$. The reaction was stirred at 60 °C for 2 h. Then, the solvent was removed under vacuum and the remaining residue was diluted with water and extracted with *t*-BuOMe and EtOAc. The combined organic layers were washed with 1 N HCl, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (hexane/*t*-BuOMe 6:4) to afford 5 mg (20%) of the corresponding nitrate derivative and 14 mg (72%) of **7**.[20]

Method B. When the mixture **16** + **7** was heated under the same conditions of lactonization employed in the previous experiment but using $AgBF_4$, only the formation of **7** (84%) was observed.

Method C. To a solution of 20 mg (0.07 mmol) of monoacid **15** in 3 mL of CH_2Cl_2 cooled at 0 °C was added 19 mg (0.075 mmol) of *m*-CPBA. The reaction mixture was stirred for 4.5 h, and during this time, the temperature increased to 0 °C. Then, the solvent was removed under vacuum and the remaining residue was purified by column chromatography (*t*-BuOMe/EtOAc 9:1) to afford 13 mg (70%) of **7**.

Method D. Diacid **8** (100 mg, 0.36 mmol) was dissolved in 1.2 mL of acetone and 0.3 mL of glacial AcOH. To this solution were added 58 mg (0.54 mmol) of *p*-benzoquinone and 20 mg (0.09 mmol) of $Pd(OAc)_2$. The mixture was stirred at room temperature for 7 d. Removal of the solvent and column chromatography of the residue afforded 56 mg (56%, 70% based on recovered starting material) of **7**.

13,14,15,16-Tetranorlabda-7,9(11)-diene-(19,6*β*),(12,17)-diolide (17). A solution of LDA (8 mmol) was prepared by adding *n*-butyllithium (3.2 mL of a 2.5 M solution in hexane, 8 mmol) to diisopropylamine (2.2 mL, 16 mmol) in THF (5 mL) at −78 °C. The resulting solution was stirred for 20 min, and dilactone **7** (430 mg, 1.56 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred for 20 min and 1.3 mL (10.4 mmol) of TMSCl was added dropwise at −78 °C. After further stirring for 20 min at −60 °C, 2 g of PhSeCl (10.4 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm over 1 h. The mixture was then diluted with *t*-BuOMe and quenched with the dropwise addition of 5% NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting selenide was used in the next reaction without purification.

The selenide was redissolved in 50 mL of CH_2Cl_2, and 3.5 mL of 30% H_2O_2 and 3.5 mL of pyridine were added. The mixture was stirred for 5 min at reflux. After being cooled to room temperature, the reaction was diluted with *t*-BuOMe and washed with 2 N HCl and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, and the resulting crude product was purified by flash chromatography to afford 345 mg (80%) of **17**. Its spectral data are identical to those previously reported.[11] HRFABMS calcd for $C_{16}H_{18}O_4Na$ [M + Na]$^+$ 297.1103, found 297.1104.

7α,8α-Epoxy-13,14,15,16-tetranorlabd-9(11)-ene-(19,6*β*),(12,17)-diolide (3). To a solution of dimethyldioxirane in acetone (10 mL) was added 25 mg (0.09 mmol) of dienediolide **17**. The mixture was stirred at room temperature for 24 h and concentrated in a vacuum. The resulting crude was redissolved in CH_2Cl_2, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (hexane/*t*-BuOMe, 4:6) afforded 5 mg (0.017 mmol, 19%, 49% based on recovered starting material) of **3**. The spectral data for **3** are identical to those reported in the literature for oidiolactone C.[21] $[\alpha]^{20}_D$ −12.0 (c = 0.2, $CHCl_3$).

Dimethyl 8-Oxo-13,14,15,16,17-pentanorlabd-6-ene-12,19-dioate (9). A solution of **4** (3.0 g, 9.9 mmol) in 50 mL of CH_2Cl_2 cooled at −78 °C was bubbled with a steam of O_2/O_3 (30 nL/h) for 3 h. Then, argon was bubbled for 10 min and 6 mL of dimethyl sulfide was added. The mixture was stirred for 6 h at room temperature and then concentrated under reduced pressure. Purification by column chromatography afforded ketone **18** (1712 mg, 65%) and alkene **10** (392 mg, 15%).

Following the same procedure described for **10**,[12] compound **18** was oxidized and esterified to give the corresponding methyl ester in 90% yield.

To a solution of 1 g (3.22 mmol) of this intermediate in 40 mL of EtOAc was added 1 g (5.23 mmol) of PhSeCl. The mixture was allowed to stir at room temperature for 60 h, and then the solvent was evaporated. The resulting selenide was redissolved in 40 mL of CH_2Cl_2, and 0.55 mL of 30% H_2O_2 and 0.64 g of pyridine were added. The mixture was stirred for 15 min at room temperature and 15 min at reflux. After being cooled to room temperature, the reaction was diluted with CH_2Cl_2 and washed with 2 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and the resulting crude product purified by flash chromatography (hexane/*t*-BuOMe 7:3) to afford 858 mg (86%) of **9** as colorless crystals: mp 60−62 °C; $[\alpha]^{20}_D$ −1040 (c = 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 10.6, 2.1 Hz, 1H), 6.01 (dd, J = 10.6, 3.2 Hz, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 2.87 (dd, J = 8.1, 4.2 Hz, 1H), 2.72 (dd, J = 16.3, 8.1 Hz, 1H), 2.50 (dd, J = 3.2, 2.1 Hz, 1H), 2.30 (br d, J = 14.0 Hz, 1H), 2.19 (dd, J = 16.3, 4.2

Hz, 1H), 1.72 (m, 1H), 1.55 (m, 2H), 1.35 (m, 1H), 1.34 (s, 3H), 1.15 (ddd, J = 13.5, 13.5, 4.0 Hz, 1H), 0.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 176.4, 173.9, 149.3, 126.8, 57.7, 55.6, 51.9, 51.8, 43.3, 43.2, 37.4, 37.0, 27.7, 27.7, 19.0, 12.2; HRFABMS calcd for $C_{17}H_{24}O_5Na$ [M + Na]$^+$ 331.1521, found 331.1512.

Methyl 13,14,15,16-Tetranorlabd-6-ene-12,8*β*-olide-19-oate (28). To a stirred solution of 710 mg (2.3 mmol) of **9** in 20 mL of dry THF was added 1.8 mL (2.5 mmol) of MeMgBr (1.4 M in hexane) dropwise. After 20 min, the reaction was diluted with *t*-BuOMe and quenched by addition of saturated aqueous NH_4Cl at 0 °C. The organic layer was subsequently washed with brine, dried (Na_2SO_4), and evaporated. The crude mixture was purified by flash chromatography using CH_2Cl_2/*t*-BuOMe 9:1 as eluent to give 564 mg (84%) of **28** as colorless crystals: mp 116−118 °C; $[\alpha]^{20}_D$ −13.0 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, J = 10.3, 1.7 Hz, 1H), 5.82 (dd, J = 10.3, 3.0 Hz, 1H), 3.61 (s, 3H), 2.78 (dd, J = 18.2, 8.9 Hz, 1H), 2.42 (d, J = 18.2 Hz, 1H), 2.28 (br d, J = 13.5 Hz, 1H), 1.94 (d, J = 8.9 Hz, 1H), 1.87 (t, J = 2.4 Hz, 1H), 1.79 (qt, J = 14.0, 3.6 Hz, 1H), 1.66 (br d, J = 13.0 Hz, 1H), 1.51 (m, 1H), 1.38 (s, 3H), 1.27 (s, 3H), 1.03 (ddd, J = 13.5, 13.5, 4.0 Hz, 1H), 0.96 (ddd, J = 13.3, 13.3, 4.1 Hz, 1H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 176.3, 130.9, 125.8, 82.2, 53.1, 51.8, 51.6, 43.1, 37.6, 37.4, 36.1, 30.9, 28.2, 27.9, 18.7, 11.8; IR (film) 1764, 1724, 1657, 700, 724 cm^{-1}; HRFABMS calcd for $C_{17}H_{24}O_4Na$ [M + Na]$^+$ 315.1572, found 315.1571.

13,14,15,16-Tetranorlabd-6-ene-12,8*β*-olide-19-oic Acid (32). To a solution of methyl ester **28** (1900 mg, 6.5 mmol) in 100 mL of DMF was added 3185 mg (32.0 mmol) of sodium propanethiolate. The mixture was stirred at 50 °C for 15 h. Cool water was added, then the mixture was acidified to pH 2 with 2 N HCl and extracted with *t*-BuOMe. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in a vacuum. Purification by flash chromatography (hexane/*t*-BuOMe 1:1) gave 1500 mg (5.4 mmol, 83%) of **32** as white solid: mp 220−222 °C; $[\alpha]^{20}_D$ −15.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (dd, J = 10.3, 1.8 Hz, 1H), 5.87 (dd, J = 10.3, 3.0 Hz, 1H), 2.82 (dd, J = 18.2, 8.9 Hz, 1H), 2.47 (d, J = 18.2 Hz, 1H), 2.29 (br d, J = 13.5 Hz, 1H), 1.98 (d, J = 8.8 Hz, 1H), 1.92 (t, J = 2.4 Hz, 1H), 1.84 (qt, J = 13.9, 3.4 Hz, 1H), 1.72 (br d, J = 13.0 Hz, 1H), 1.55 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.08 (ddd, J = 13.5, 13.5, 4.1 Hz, 1H), 1.00 (ddd, J = 13.3, 13.2, 4.0 Hz, 1H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8, 176.3, 130.6, 126.1, 82.3, 53.2, 51.9, 43.0, 37.6, 37.0, 36.4, 30.9, 28.24, 28.19, 18.7, 12.0; IR (film) 3625−2590 (wide band), 1750, 1693, 721 cm^{-1}; HRFABMS calcd for $C_{16}H_{22}O_4Na$ [M + Na]$^+$ 301.1416, found 301.1416.

12-Hydroxy-13,14,15,16-tetranorlabd-7-ene-19,6*β*-olide (34). A suspension of 1400 mg (37 mmol) of $LiAlH_4$ in 60 mL of THF was cooled to 0 °C. A solution of acid **32** (1500 mg, 5.4 mmol) in THF (70 mL) was added dropwise. After complete addition, the mixture was stirred at 0 °C for 9 h. The reaction was diluted with *t*-BuOMe and the pH of the reaction adjusted to 2 by the dropwise addition of 1 N HCl.The resulting mixture was stirred at room temperature for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc. Purification by flash chromatography (hexane/*t*-BuOMe 3:7) afforded 1262 mg (88%) of **34** as colorless crystals: mp 78−80 °C; $[\alpha]^{20}_D$ −8.5 (c = 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6) δ 5.74 (1H, m), 4.84 (m, 1H), 3.71 (m, 1H), 3.54 (m, 2H), 1.98 (m, 2H), 1.84 (t, J = 1.5 Hz, 3H), 1.69−1.21 (m, 7H), 1.25 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ_182.3, 145.6, 119.9, 74.0, 63.3, 51.4, 48.2, 43.4, 34.9, 34.0, 30.5, 29.0, 24.1, 22.2, 18.8, 18.6; IR (film) 3441 (wide band), 1767, 1646, 848, 799 cm^{-1}; HRFABMS calcd for $C_{16}H_{24}O_3Na$ [M + Na]$^+$ 287.1623, found 287.1622.

Methyl 13,14,15,16-Tetranorlabd-7-ene-19,6*β*-olide-12-oate (27). To a solution of 330 mg of alcohol **34** (1.24 mmol) in 22 mL of DMF were added 4671 mg (12.4 mmol) of PDC and 4 Å molecular sieves. The reaction was stirred at room temperature for 21 h. Water was added and the resulting mixture was extracted with *t*-BuOMe. The combined extracts were washed with brine, dried over Na_2SO_4, and filtered. The solution that resulted was esterified with CH_2N_2 in *t*-BuOMe and concentrated in a vacuum. The residue was purified by flash chromatography (hexane/*t*-BuOMe 4:1) to afford 272 mg (75%) of **27**, together with 26 mg (8%) of the corresponding aldehyde, which could be further oxidized, and 54 mg (15%) of lactone **28**, which could also be recycled. Methyl ester **27** was isolated as colorless crystals: mp 79−81 °C; $[\alpha]^{20}_D$ −2.0 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 4.83 (m, 1H), 3.69 (s, 3H), 2.58 (m, 1H), 2.34 (s, 1H), 2.09 (m, 1H), 1.81 (d, J = 5.1 Hz, 1H), 1.71 (m, 1H), 1.70 (d, J = 1.1 Hz, 3H), 1.51 (m, 3H), 1.30 (m, 1H), 1.29 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 174.4, 143.3, 119.2, 73.4, 52.0, 50.8, 47.5, 42.8, 33.7, 33.4, 31.4, 28.0, 24.0, 21.4, 18.5, 18.0; IR (film) 1767, 1736, 1651, 826 cm^{-1}; HRFABMS calcd for $C_{17}H_{24}O_4Na$ [M + Na]$^+$ 315.1572, found 315.1572. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.62; H, 8.82. Found: C, 69.86; H, 8.42.

13,14,15,16-Tetranorlabd-7-ene-(19,6*β*),(12,17)-diolide (7). Method E. To a solution of 473 mg (1.6 mmol) of methyl ester **27** in 17 mL of glacial AcOH was added 355 mg of SeO_2 (3.2 mmol). The mixture was stirred at reflux for 30 min. The reaction was then diluted with *t*-BuOMe and washed with saturated $NaHCO_3$ and brine. The mother liquors were neutralized and reextracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in a vacuum. Purification by flash chromatography afforded 225 mg (51%) of dilactone **7** identical to that prepared above.

Acknowledgment. This research was supported by the Spanish Dirección General de Investigación Científica y Técnica (DGICYT; Proyecto PB 98-1365).

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for all new compounds that appear as title compounds. This material is available free of charge via the Internet at http://pubs.acs.org

JO0161882