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A Convenient Synthesis of A-Ring-Functionalized Podolactones. Revision of the Structure of Wentilactone B

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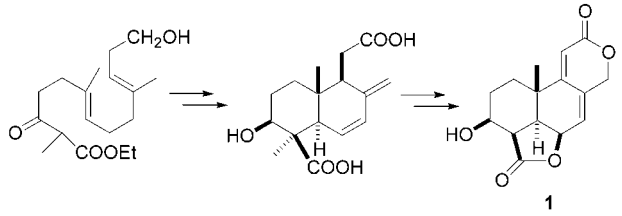
ABSTRACT



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A new route to podolactones functionalized in the A ring has been achieved. Two key steps were employed in this synthesis, the construction of the bicyclic skeleton via a Mn(III)-mediated radical cyclization and the transformation of this bicyclic intermediate into the tetracyclic podolactone skeleton through a Pd (II)-mediated bislactonization of the corresponding conjugate diene. The reported synthesis of 3β-hydroxy-13,14,15,-16-tetranorlabda-7,9(11)-dien-(19,6β),(12,17)-diolide (1) let us reassign the structure of wentilactone B, for which structure 1 was wrongly reported.

Podolactones are nor- or bisnorditerpenic compounds isolated from different plants of the genus *Podocarpus*[1] and from filamentous fungi.[2] These molecules present a wide range of biological activities, with antitumor, insecticidal, antifeedant, allelopathic, and fungicide activities deserving special attention.[3] With respect to this antifungal activity, it is worth mentioning that some of these compounds have shown promising results against *Candida albicans* and the dimorphic fungus *Histoplasma capsulatum*, which causes one of the most severe mycoses.[3e] Recently, the production of terpenoid lactones from *Oidiodendrum griseum*,[4] and its use as an antiinflammatory in the treatment of IL-1 (interleukin-1) and TNF (tumor necrosis factor)-mediated diseases has been described. Since we have previously reported the synthesis of podolactones with no functionalization in the A ring,[5] we aimed to complete the access to most of these natural dilactones by seeking a methodology to prepare 3β-hydroxy derivatives, compounds whose preparation has only been reported once.[6] Here we describe the synthesis of 3β-

(1) In *Dictionary of Terpenoids*; Connolly, J. D., Hill, R. A. Eds.; Chapman & Hall: London, U.K., 1991; Vol. 2, pp 853−857.

(2) (a) Andersen, N. R.; Rasmunsen, P. R. *Tetrahedron Lett.* **1984**. (b) Dorner, J. W.; Cole, R. J.; Springer, J. P.; Cox, R. H.; Cutler, H.; Wicklow, D. T. *Phytochemistry* **1980**, *19*, 1157. (c) Ellestad, G. A.; Evans, R. H.; Kunstmann, M. P.; Lancaster, J. E.; Morton, G. O. *J. Am. Chem. Soc.* **1970**, *92*, 5483.

(3) (a) Hembree, J. A.; Chang, C.; McLaughlin, J. L.; Cassady, J. M.; Watts, D. J.; Wenkert, E.; Fonseca, S. F.; De Paiva Campello, J. *Phytochemistry* **1979**, *18*, 1691. (b) Singh, P.; Russell, G. B.; Hayashi, Y.; Gallagher, R. T.; Fredericksen, S. *Entomol. Exp. Appl.* **1979**, *25*, 121. (c) Zhang, M.; Ying, B. P.; Kubo, I. *J. Nat. Prod.* **1992**, *55*, 1057. (d) Macías, F. A.; Simonet, A. M.; Pacheco, P. C.; Barrero, A. F.; Cabrera, E.; Jiménez-González, D. *J. Agric. Food Chem.* **2000**, *48*, 3003. (e) Hosoe, T.; Nozawa, K.; Lumley, T. C.; Currah, R. S.; Fukushima, K.; Takizawa, K.; Miyaji, M.; Kawai, K. *Chem. Pharm. Bull.* **1999**, *47*, 1591.

(4) Ichikawa, K.; Ikunaka, M.; Kojima, N.; Nishida, H.; Yoshikawa, N. European Patent 0 933 273 A1, 1999.

(5) Barrero, A. F.; Quílez del Moral, J. F.; Cuerva, J. M.; Cabrera, E.; Jiménez-González, D. *Tetrahedron Lett.* **2000**, *41*, 5203.

(6) To our knowledge, only one A-ring-functionalized podolactone, (±)3β-hydroxynagilactone F, has been previously synthesized. This synthesis was reported by de Groot et al. in less than 0.1% yield: Reuvers, J. T. A.; de Groot, A. *J. Org. Chem.* **1986**, *51*, 4594.

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hydroxy-13,14,15,16-tetranorlabda-7,9(11)-dien-(19,6β),(12,-17)-diolide (**1**), a structure that was wrongly attributed to wentilactone B.[2b]

The retrosynthetic planning for **1** is shown in Figure 1. This scheme includes as key steps the radical cyclization of

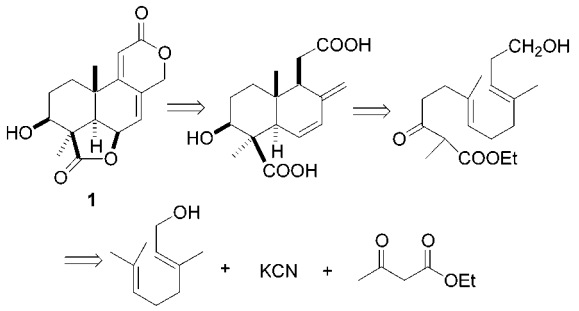
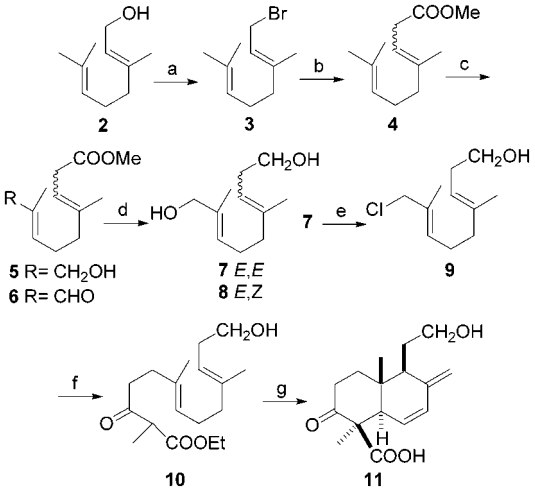


Figure 1. Retrosynthetic analysis of 3β-hydroxy-13,14,15,16-tetranorlabda-7,9(11)-dien-(19,6β),(12,17)-diolide (**1**).

the acyclic precursor and the 1,4-regioselective oxidation of the appropriate conjugated diene in the presence of Pd(II) complexes.[7]

The preparation of the bicyclic intermediate **11** is summarized in Scheme 1. Bromination of commercially available geraniol (**2**) with PBr_3 afforded bromide **3**, which upon treatment with KCN and subsequent hydrolysis and esterification furnished **4** as a mixture of geometrical isomers (this

Scheme 1[a]



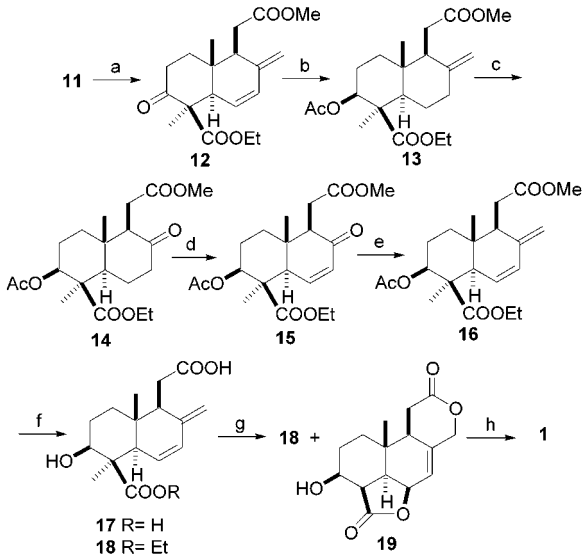
[a] Regents and conditions: (a) (i) PBr_3, *t*-BuOMe, 0 °C, 25 min; (ii) KCN, DMSO, 2 h, 80%; (b) (i) KOH 25%, MeOH, 90 °C, 9 h; (ii) CH_2N_2, ether, 0 °C, 5 min, 68% of **3** and **4** (ratio 4:1) in two steps; (c) SeO_2, *t*-BuOOH, CH_2Cl_2, 5 °C, 6 h, 65%; (d) LAH, THF, 0 °C → rt, 12 h, 86% of **7** and **8** (ratio 4:1); (e) (i) NCS, DMS, CH_2Cl_2, 0 °C, 2.5 h, 85%; (f) $CH_3COCHCH_3COOEt$, NaH, *n*-BuLi, THF, 2.5 h, 79%; (g) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, HOAc, 68%

mixture could only be separated as the diol derivatives **7** and **8**). Allylic oxidation of **4** with SeO_2 gave a mixture of **5** and **6**, which was converted by treatment with LAH to diols **7** and **8** in a 4:1 ratio favorable to the *E*,*E* isomer. Regioselective chlorination of **7** yielded the corresponding chloride **9**.[8] Alkylation of the dianion of ethyl 2-methylacetoacetate with **9** afforded 79% of acyclic precursor **10**. Oxidative free-radical cyclization of **10** using a 2:1 molar ratio of $Mn(OAc)_3$ and $Cu(OAc)_2$[9] in deaerated AcOH provided 68% of bicyclic **11**.[10]

Following the same process as described for **7**, compound **8** was converted into the corresponding *E*,Z acyclic precursor. As expected,[11] no bicyclic compound was obtained upon treatment of this precursor with Mn(III).

The remaining steps for the synthesis of **1** are shown in Scheme 2. Oxidation of **11** with PDC in DMF followed by

Scheme 2[a]



[a] Regents and conditions: (a) (i) PDC, DMF, 24 h; (ii) CH_2N_2, ether, 75% in two steps; (b) (i) $NaBH_4$, MeOH, 0 °C, 15 min, 91%; (ii) ClOAc, DMAP, 20 h, 95%; (c) (i) O_3, CH_2Cl_2, −78 °C, 20 min; (ii) PPh_3, −78 °C → rt, 2 h, 91%; (d) (i) PhSeCl, EtOAc, 60 h, (ii) H_2O_2, Py, CH_2Cl_2, 0 °C → rt, 15 min, 77%; (e) Tebbe's reagent, THF, 0 °C, 17 min, 69%; (f) $NaSCH_2CH_2CH_3$, DMF, 50 °C, 26 h, 95%; (g) $Pd(OAc)_2$, *p*-benzoquinone, HOAc, acetone, 18 h, 78% of **19** based on the amount of **17** in the mixture of **17** and **18**; (h) (i) LDA, −78 °C, THF, 20 min; (ii) TMSCl 20 min; (iii) PhSeCl, −60 °C, THF, 45 min; (iv) H_2O_2, Py, CH_2Cl_2, 30 s, 40 °C, 36%.

CH_2N_2 treatment yielded methyl ester **12**, which was converted to acetate **13** after standard transformations.

(7) (a) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (b) Bäckvall, J. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Stang, P.. Diederich, F., Eds.; Wiley-VCH: Weinham, 1998; pp 339−385.

(8) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 5203.

(9) Oxidative radical cyclization of polyenes with Mn(III) and Cu(II) has been widely used in the synthesis of policyclic compounds. For recent examples see: (a) Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785 and references therein. For a review, see: (b) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

Ozonolysis of **13** furnished ketone **14** in high yield, which upon treatment with PhSeCl in EtOAc and oxidation with H_2O_2 provided conjugated ketone **15**. In a noteworthy transformation, **15** was chemoselectively methylenated by exposure to Tebbe reagent[12] to afford **16**. Subsequent saponification with sodium propanethiolate afforded the mixture of the desired dicarboxylic compound **17** and monoester **18** (1:1.4 ratio). Regioselective bislactonization of **17** took place when the mixture was subjected to the presence of substoichiometric Pd(II) (25%) and *p*-benzoquinone in a mixture of acetic acid and acetone as solvent (Figure 2).[13] Ester **18** could be recovered and recycled.

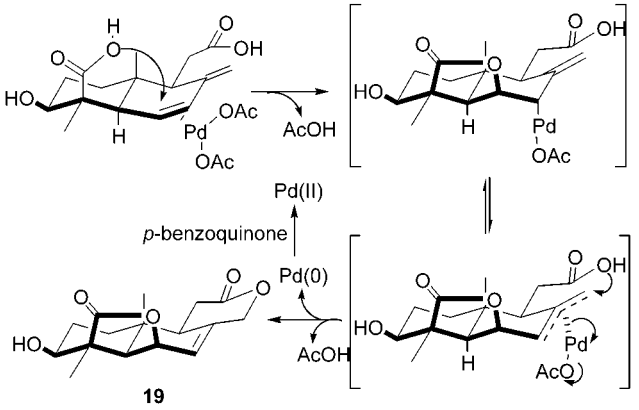


Figure 2. Proposed mechanism for the bislactonization of **14**.

Introduction of the C9−C11 unsaturation proceeded, via the corresponding silyl ketene acetal, after *syn* elimination of the 11α-phenilselenoxide intermediate by treatment with hydrogen peroxide. It is worth mentioning that under the reaction conditions the free hydroxyl group at C-3 remained unaltered, surely as a result of the formation of hydrogen bonding between the hydroxyl hydrogen atom and the carbonyl oxygen atom of the ester group at C4.

Surprisingly, the NMR data of our synthetic **1** do not match with those reported for natural podolactone wentilactone B, to which the same chemical structure was assigned[2b]. The kind donation of a sample of wentilactone B by Professor Dorner allowed us to record high-resolution NMR spectra for this compound, whose analysis both confirmed the wrong assignation of the natural product structure and let us relocate the hydroxyl group in the 2α-position. This reassignment is confirmed by comparison of the newly recorded NMR data of wentilactone B with those of 2α-hydroxynagilactone F (**20**) (Table 1).[14]

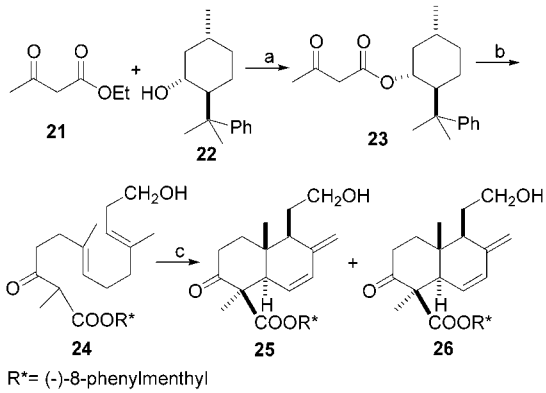
Table 1. ^{1}H NMR of **1**, Wentilactone B, and 2α-Hydroxynagilactone F (**20**)[a]

H	1	wentilactone B[b]	20
1α	2.15−1.65 m	1.82 dd (4.9, 13.5)	1.95
1*β*	2.15−1.65 m	2.09 t (13.5)	2.24t (13.0)
2	2.15−1.65 m	4.11 m	4.11 m
3α	3.79 m	1.54 dd (7.0, 13.5)	1.59 dd (7.0, 14.0)
3*β*		2.41 dd (9.0, 13.5)	2.45 dd (9.0, 14.0)
5	2.18 d (4.1)	2.15 d (5.2)	1.95 d (5.0)
6	5.22 bt (4.0)	5.18 td (1.6, 4.9)	5.08 bt (1.5, 5.0)
7	6.36 m	6.35 dd (1.6, 5.0)	6.20 dd (1.5, 5.0)
11	5.72 d (1.8)	5.74 d (1.7)	5.83 d (1.6)
17α	4.97 d (13.8)	4.95 d (13.5)	
17*β*	5.08 dt (1.9, 13.8)	5.04 dt (1.9, 13.5)	4.87 d (1.8)
18	1.53 s	1.38 s	1.42 s
20	0.92 s	1.22 s	1.28 s

[a] Coupling constant in hertzs are given in brackets. [b] Newly recorded data.

With the ultimate aim of achieving enantioselective syntheses of the target compounds, we also studied the diastereoselectivity of the cyclization step using (−)-8-phenylmentol as a chiral auxiliary.[15] Preparation of the chiral acyclic precursor is depicted in Scheme 3.

Scheme 3[a]



[a] Regents and conditions: (a) DMAP, toluene, reflux, 75%; (b) NaH, *n*-BuLi, THF, **9**, 2.5 h, 80%; (c) $Mn(OAc)_3 \cdot 2H_2O$, $Cu(OAc)_2 \cdot H_2O$, HOAc, 7.5 h, 45%.

Transesterification of ethyl 2-methylacetoacetate (**21**) with (−)-8-phenylmentol (**22**) in the presence of DMAP afforded

(10) The cyclization of **10** to give **11** in 58% yield has been previously reported by Zoretic et al. in their synthesis of *d*,*l*-norlabdane oxide: Zoretic, P. A.; Haiquan, F.; Ribeiro, A. A. *J. Org. Chem.* **1998**, *63*, 4779.

(11) Radical cyclization has been described to proceed with total stereoselectivity. Furthermore, in works published by us and others, double bonds with *Z* configuration have been reported not to react with free radicals: (a) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074. (b) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.

(12) In *Handbook of Reagents for Organic Synthesis. Reagents, Auxiliaries, and Catalysts for C−C Bond Formation*; Coates, R. M., Denmark, S. E., Eds.; John Wiley & Sons Ltd: Chichester, 1999; pp 180−184.

(13) (a) Although few examples of intramolecular nucleophilic attack of a carboxylate to conjugate dienes leading to a monolactone have been described (Jonasson, C.; Rönn, M.; Bäckvall, J. E. *J. Org. Chem.* **2000**, *67*, 2122), this bislactonization process has been successfully applied only once before by our group in the synthesis of oidiolacone C: Barrero, A. F.; Arseniyadis, S.; Quílez del Moral, J. F.; Herrador, M. M.; Valdivia, M.; Jiménez, D. *J. Org. Chem.* **2002**, in press. (b) Bäckvall, J. E.; Granberg, K. L.; Andersson, P. G.; Gatti, R.; Gogoll, A. *J. Org. Chem.* **1993**, *58*, 5445.

(14) Kubo, I.; Himejina, M.; Ying, B. P. *Phytochemistry* **1991**, *30*, 1469.

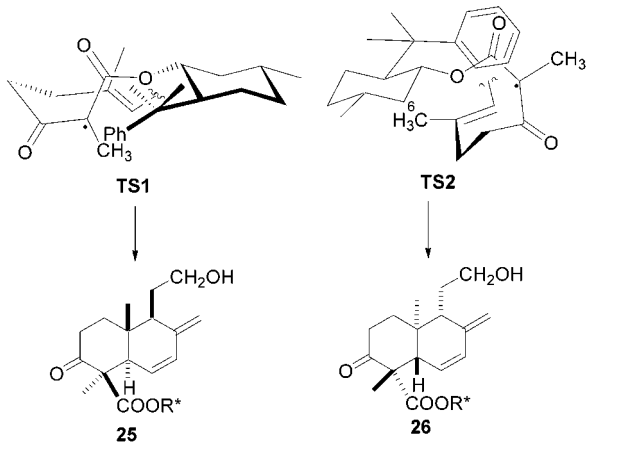


Figure 3. Proposed charlike transition states for free radical cyclization of **24**.

23. As described for the formation of the racemic acyclic precursor, alkylation of the dianion of **23** with **9** afforded 79% of **24**. When the radical cyclization is achieved at 25 °C in HOAc, the induced selectivity is low (**25** and **26** were obtained in 2:1 ratio). However, if the reaction is carried out in MeOH at 0 °C the selectivity increases, and a 6.5:1 mixture of diastereomers is obtained.

The determination of the stereochemistry for the cyclization compounds has been realized on the grounds of the spatial disposition of the two more favorable chairlike transition states (Figure 3). The assignment of **25** as major diastereomer has been made considering the steric interaction in TS2 between the methyl substituent on the double bond and the 6-CH_2 group of the menthyl moiety.[15a]

In conclusion, with the synthesis of 3β-hydroxy-13,14,-15,16-tetranorlabda-7,9(11)-dien-(19,6β),(12,17)-diolide (**1**) we have described a new access to 3β-hydroxypodolactones, which together with the recent syntheses reported by our group widens the range of podolactone types available by chemical synthesis. The asymmetric version of this synthesis has also been investigated. This work has also allowed us to reassign the structure of natural wentilactone B.

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Supporting Information Available: Experimental procedures and spectroscopic data of all new compounds. This material is available free of charge at http://pubs. acs.org.

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(15) (−)-8-Phenylmenthol has been reported both to induce a good diastereomer ratio and to proceed with high yield in Mn(III)-based asymmetric radical cyclization of related β-keto esters; see: (a) Yang, D.; Ye, X.-Y.; Xu, M. *J. Org. Chem.* **2000**, *65*, 2208. (b) Zhang, Q.-W.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B. M.; Snider, B. B.. *J. Org. Chem.* **1993**, *58*, 7640. (c) Zoretic, P. A.; Weng, X.; Biggers, M. S.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1992**, *33*, 2637.