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# Synthesis and Structural Reassignment of Plakinidone

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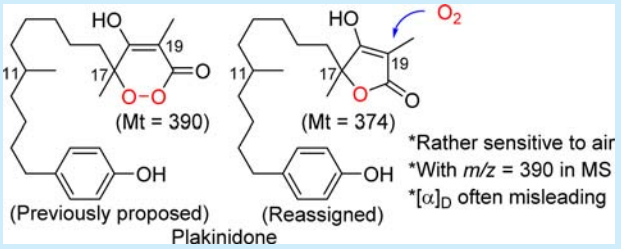
Supporting Information

**ABSTRACT:** In connection with its first synthesis, plakinidone was structurally revised to a five-membered lactone. The key evidence for the previous assignment of this natural product as a perlactone was proven to be a misinterpretation of the MS data because of unawareness of a facile air oxidation. The synthetic samples also allowed for detection of differences in $^{13}C$ NMR for diastereomers of remote stereogenic centers, along with the influence of the air oxidation on the optical rotation.




The marine sponges of the genus *Plakortis* are a rich source of cyclic peroxides.[1] To date, nearly 100 such peroxides have been isolated from various species of *Plakortis*. Essentially all of the cyclic peroxides generated by *Plakortis* are either five- or six-membered, with an ethereal link on both oxygen atoms of the peroxy bonds, constituting a major family of cyclic organic peroxides. This, along with the various bioactivities (including antitumor and antiparasitic activities) already shown in a number of cases, promoted the appearance of many elegant synthetic approaches that are applicable to most (if not all) of the known structural patterns of the peroxy functionalities in this family.[2]

During our study of organic peroxides, plakinidone[3a] (**1**, Figure 1), an exception to all other cyclic peroxides from

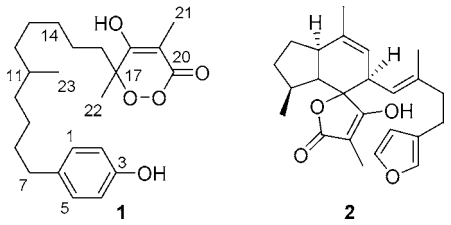


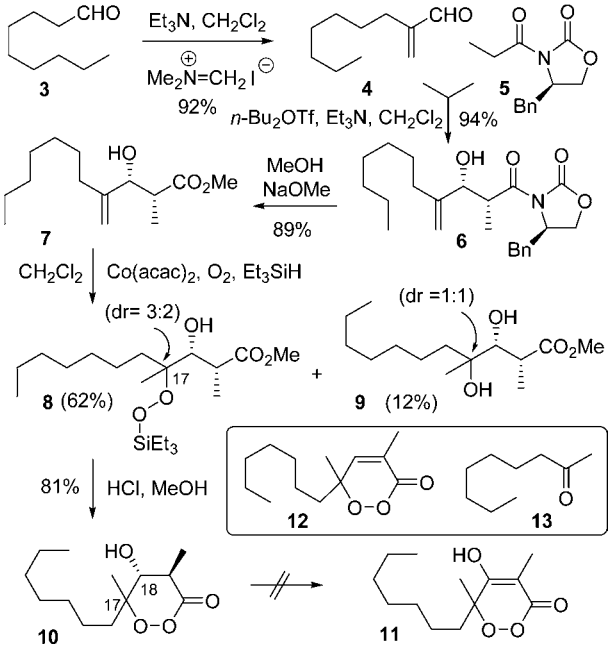

**Figure 1.** Structure originally proposed for plakinidone (**1**) and ircinianin (**2**), the reference compound for the assignment of a six-membered perlactone ring in plakinidone (cf. ref 3a).

*Plakoritis*, caught our attention. As mentioned[3] in the original report, this was the first natural six-membered perlactone ever identified. In fact, only two other natural perlactones (both being eight-membered ones) can be found in the literature to date,[4] one of which[4b] was later proven[4c] to be erroneously assigned. These factors indicated that natural perlactones are extremely rare; confirmation of the previously assigned structure for **1**, establishment of its absolute configuration, and development of an entry to a structural motif of the plakortis peroxides not covered yet by the existing syntheses[2] thus appeared warranted.

Because the perlactone moiety in **1** is five $CH_2$ units away from the C11 stereogenic center[5] and the remainder of the molecule, it seemed that a model compound with a simple alkyl at the C17 would show NMR and optical rotation close to those for natural **1**. Therefore, to access the core structure as quickly as possible we began with a synthesis of perlactone **11**.

As shown in Scheme 1, commercially available **3** was treated with Eschenmoser's[6] salt to furnish known[7] **4**, which was further transformed into **6** using Evans' asymmetric aldol condensation. The chiral auxiliary was then removed with NaOMe. The resulting ester **7** was treated with $O_2/Et_3SiH/Co(acac)_2$[8] to install the peroxy functionality (disappointedly, with poor

**Scheme 1**

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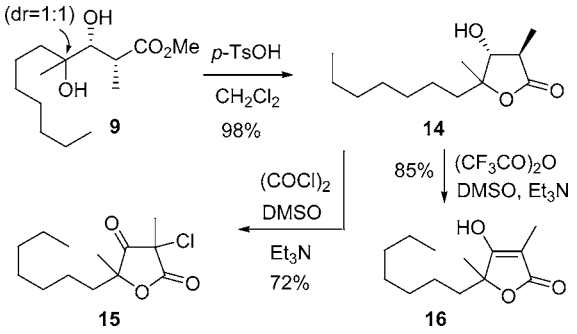
stereoselectivity). Desilylation and lactonization led to **10** as expected. However, subsequent oxidation of the C18 hydroxyl group to afford **11** affected many broadly employed oxidation protocols including Swern,[9] Dess–Martin,[10] IBX/DMSO,[11] TPAP/NMO,[12] PCC/NaOAc,[13] TEMPO/NaOCl/KBr,[14] TEMPO/PhI(OAc)$_2$,[15] TEMPO/Oxone,[16] TEMPO/*m*-CPBA,[17] and AZADO/PhI(OAc)$_2$.[18] In most cases, the starting **10** was fully consumed, leading to rather polar/unidentifiable products. Only when TEMPO/PhI(OAc)$_2$ was used as the oxidant did we manage to identify two of the minor products **12** and **13**. The desired **11** was never detected.

The repeated failures prompted us to suspect whether the assignment of **1** was incorrect. Upon closer inspection, we found the MS and NMR evidence for the structure of **1** to be unconvincing; in particular, the NMR discrepancies between **1** and **2** (ircinianin[3b]) did not necessarily disprove a five-membered lactone moiety. Therefore, we next turned our attention to **16**.

As shown in Scheme 2, lactonization of **9** led to **14**. Although subsequent oxidation under typical Swern conditions gave **15**, the desired **16** was eventually obtained using $(CF_3CO)_2O$ instead of $(COCl)_2$.

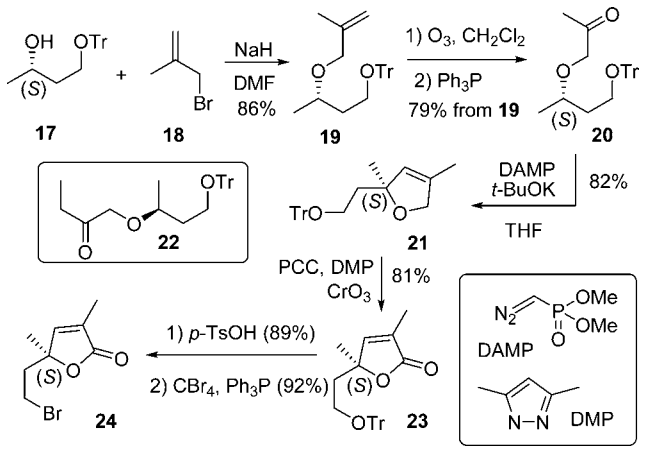
**Scheme 2**




Lactone **16** indeed showed $^1$H and $^{13}$C NMR reasonably close to those for the corresponding moieties in natural **1**. Therefore, we next decided to aim at a modified target structure, which has a five-membered lactone instead of the perlactone.

The lactone fragment of the modified target was then synthesized as shown in Scheme 3. Alkylation of the known[19] **17** with **18** gave **19**, which on treatment with $O_3$ and $Ph_3P$ afforded **20**. Subsequent treatment with $Me_3SiCHN_2$/*n*-BuLi[20a]

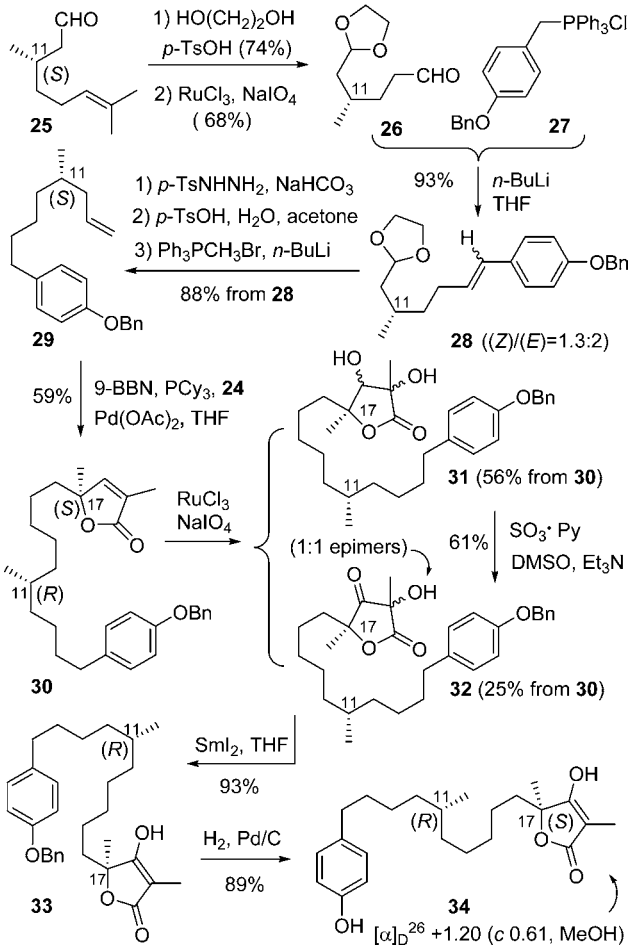
**Scheme 3**




led to the desired **21** in 65% yield, along with 24% of **22** (an unprecedented case of carbine insertion into linear ketone alkyl group[20b]). When DAMP/*t*-BuOK[21] ws used as the reagent, the yield for **21** was raised to 82% (without any **22** formed). Oxidation under the $CrO_3$/PCC/DMP[22] conditions afforded lactone **23** smoothly. Cleavage of the trityl group in **23** followed by treatment with $CBr_4/Ph_3P$ gave the desired bromide **24**.

The C1–C12 fragment was synthesized as shown in Scheme 4. Conversion[23] of citronellal **25** into aldehyde **26** and subsequent

**Scheme 4**




Wittig reaction with **27** furnished **28** as a 1.3:2 mixture of (*Z*)- and (*E*)-isomers. Saturation of the C–C double bond with diimide[24] followed by hydrolysis of the acetal and the Wittig condensation afforded alkene **29**.

A Suzuki coupling[25] of **24** and **29** was then performed to afford **30** (Scheme 4). Subsequent oxidation with $RuCl_3/NaIO_4$[25] led to diol **31** (56%) and ketone–alcohol **32** (25%). The diol could be further oxidized to **32** with $SO_3$·Py/DMSO/$Et_3N$. The redundant hydroxyl group was then removed by reduction[26] with $SmI_2$. Finally, hydrogenolysis of the benzyl protecting group over Pd/C afforded the end product **34**.

Isolation and characterization of **34** were unexpectedly difficult; the yield varied erratically from run to run, with annoying additional signals "persisting" in the $^1$H and $^{13}$C NMR spectra despite repeated chromatography. TLC monitoring revealed that some minor species formed from **34** at ambient temperature within ca. 1 h if no precautions were taken to exclude air.



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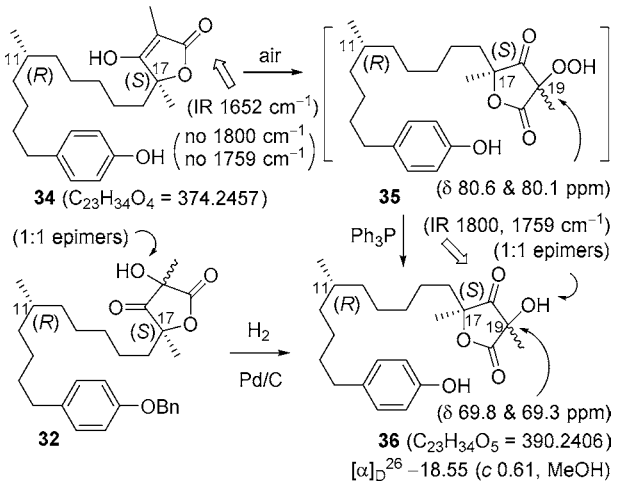
Treatment of **34** containing those readily formed impurities with $Ph_3P$ allowed for isolation of **36** (also attainable by debenzylation of **32**, Scheme 5). This, along with the $\delta$ 80.6 and

**Scheme 5**




80.1 ppm signals for the C19 in $^{13}C$ NMR for the crude mixture (cf. the 69.8 and 69.3 ppm in **36**), revealed a facile[27] air oxidation of **34** leading to **35** (unstable, tending to decompose to give **36**). Spontaneous generation of **36** also occurred during EI-HRMS analysis: even pure **34** ($C_{23}H_{34}O_4$) still showed a distinct signal at $m/z$ = 390.2408 ($C_{23}H_{34}O_5$); the critical piece of evidence for the assignment of plakinidone as a perlactone in the previous[3] study was thus proven to be a misunderstanding.

Exclusion of air from the NMR solvent effectively reduced the extra signals in $^{13}C$ NMR of **34**, giving a rectified spectrum that agreed very well with that for natural plakinidone (cf. Table S-1, Supporting Information). It was thus concluded that natural plakinidone and **34** must have the same planar structure.

Determination of configurations for plakinidone was unexpectedly difficult. In principle, either **34** or *epi*-**34** (Figure 2)

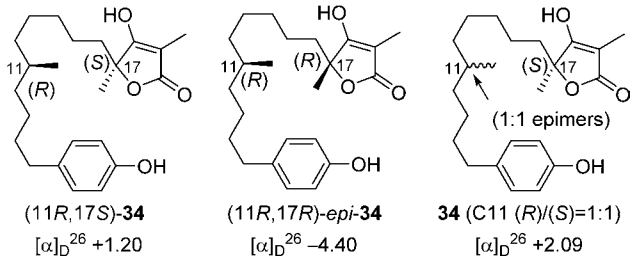



**Figure 2.** Diastereomers of **34** and their $[\alpha]_D$ measured at $c$ = 0.61 in MeOH. For the synthesis of *epi*-**34** and C-11 racemic **34** (which showed the contribution of each stereogenic center to the observed optical rotation); see the Supporting Information.

should possess the same relative configuration as plakinidone and thus must have the same magnitude for the $[\alpha]_D$. However, the specific rotation for **34** (practically free from **36**) was determined to be +1.20 ($c$ 0.61, MeOH), while the corresponding data for *epi*-**34** were −4.40 ($c$ 0.61, MeOH); neither was compatible with the $[\alpha]_D$ +7.9 for natural plakinidone and thus made the configuration assignment a "mission impossible".

Then, enlightened by the newly identified air oxidation of **34** and the IR data for the natural sample (1800 and 1760 $cm^{-1}$, Scheme 5), we envisaged that the natural sample might be substantially oxidized[28] and thus attempted to establish the configurations for natural plakinidone through the $[\alpha]_D$ for the partially oxidized samples.[29]

The $[\alpha]_D$ for **34** and *epi*-**34** was then measured at ca. 10 h after the first measurement of each sample, respectively, without any precautions to exclude air (to mimic the apparent optical rotation of the natural sample under the influence of the previously unnoticed air oxidation, cf. Supporting Information). Two diastereomers indeed behaved differently; **34** gave an apparent $[\alpha]_D$ of −2.84 (too small in magnitude), whereas *epi*-**34** showed a value of −9.3 (rather close in magnitude to 7.9), suggesting that natural plakinidone is more likely to have the same relative configuration as *epi*-**34**, although the absolute configuration is opposite according to the sign for $[\alpha]_D$.

The C11 racemic **34** showed two sets of resolved signals in $CDCl_3$ but (but not in $CD_3OD$) at 36.5/36.4 ppm and 26.75/26.78 ppm, respectively (cf. Supporting Information, Table S-6), revealing an unexpected mutual differentiation between two remote stereogenic centers.[30] Because the resolved lines matched the corresponding signals from **34** and *epi*-**34**, respectively, this interesting phenomenon might be exploitable in determination of the absolute configuration of natural plakinidone when a natural sample is available.

In summary, the first synthesis of plakinidone was achieved. En route to the synthesis, a so far unrecognized facile air oxidation was identified that not only revealed the previous misinterpretation of the MS signal but also helped detect the errors in the NMR and optical rotation data.[31] With the aid of the synthetic samples, the structure of natural plakinidone was reliably revised, while the absolute configuration was tentatively assigned as (11*S*,17*S*) on the basis of the estimation of oxidation-associated changes in the optical activity.[32] The mutual differentiation in $^{13}C$ NMR between two remote stereogenic centers observed here may also be exploitable in configuration assignments of similar alkyl-only centers (rather difficult due to lack of heteroatoms/functional groups in vicinity). Finally, the unique (to our knowledge) carbine insertion into the linear ketone alkyl group, the outcome of using $(CF_3CO)_2O$ in oxidation of **14** instead of $(COCl)_2$, and the phenol-accelerated air oxidation of five-membered enol lactones[27] also deserve particular attention.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02599.

Experimental procedures, spectroscopic data listing/scanned spectra for products (new compounds), $^{13}C$ NMR data comparison tables, and time/concentration-dependent optical rotation data for **34** (PDF)

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### Notes

The authors declare no competing financial interest.

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(27) Although **16** is much more stable than **34**, in the presence of added equal molar amounts of PhOH the air oxidation also became significant. Without any "built-in" or added phenol, similar 5-membered enol lactones in previous studies never suffered this air oxidation; cf.: (a) Bühler, H.; Bayer, A.; Effenberger, F. *Chem. - Eur. J.* **2000**, *6*, 2564−2571. (b) Desmaele, D. *Tetrahedron* **1992**, *48*, 2925−2934. (c) Takaiwa, A.; Yamashita, K. *Agric. Biol. Chem.* **1983**, *47*, 429−430.

(28) The consistency of the NMR in ref 3a with those for **34** indicated that oxidation of the natural sample occurred after the acquisition of NMR data (before recording the $[\alpha]_D$ and IR). It seems reasonable to presume that NMR were recorded before $[\alpha]_D$ and IR.

(29) In the absence of any natural sample, this appeared to be the only feasible way to gain knowledge of the configuration of natural plakinidone.

(30) The C18 OH appeared essential for this effect because the C11 of racemic **30** (without the C18 OH) failed to resolve. However, it should be noted that **34** is much more soluble in $CD_3OD$ than in $CDCl_3$. Use of (deaired) $CD_3OD$ as the solvent gave $^{13}C$ NMR of much better quality.

(31) It is not rare to use MS data as the critical evidence for the existence of peroxy bond(s) in identification of natural peroxides (cf. ref 33a). To avoid errors similar to that in the present case, inclusion of reductive degradation (as in, e.g., ref 32b) is better performed if possible.

(32) Small optical rotations measured at low concentrations (e.g., $c$ = 0.01) may be unreliable, leading to confusion in the determination of absolute configurations. See, e.g.: Yong, K. W. L.; Barnych, B.; De Voss, J. J.; Vatèle, J.-M.; Garson, M. J. *J. Nat. Prod.* **2012**, *75*, 1792−1797.

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