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Plakortolide Stereochemistry Revisited: The Checkered History of Plakortolides E and I

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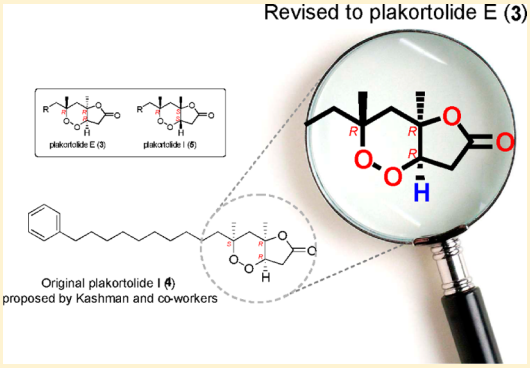
Supporting Information

ABSTRACT: The relative configuration of the plakortolide metabolite (**4**) isolated from a Madagascan *Plakortis* sp. and named (+)-plakortolide I is revised following reassignment of the ^{13}C signals for C-7 and C-16, thereby establishing that the metabolite isolated was likely (+)-plakortolide E (**3**). We propose that the name "plakortolide I" should be retained for the plakortolide metabolite **5** first isolated by the Faulkner group; its enantiomer **4** can then be named *ent*-plakortolide I in line with the description of Barnych and Vatèle. The spectroscopic data for MPA esters prepared from synthetic samples of *seco* derivatives of plakortolide E (**3**) and *ent*-plakortolide I (**4**) were compared with those of MPA esters of *seco* derivatives from naturally isolated plakortolides L (**1**) and K (**2**) and of *seco*-plakortolide E (**6a**). Likewise, the spectroscopic data for MTPA esters derived from **3** and **4** were compared with data for the MTPA esters derived from **5**. These various comparisons established that the sign of the specific rotation associated with the natural isolates is an unreliable indicator of absolute configuration and verify that the absolute configurations of plakortolides L (**1**), K (**2**), E (**3**), and I (**5**) are (3*S*, 4*S*, 6*S*), (3*R*, 4*R*, 6*S*), (3*R*, 4*R*, 6*R*), and (3*S*, 4*S*, 6*R*), respectively.



Our detailed study of the Australian marine sponge *Plakinastrella clathrata* Kirkpatrick, 1900 has revealed that this sponge is a rich source of plakortolide metabolites possessing a $Ph(CH_2)_{12}-$ side chain, their peroxy ring-opened (*seco*) derivatives, and stereochemically related plakortone ethers.[1] In addition, the sponge extract contained $Ph(CH_2)_{10}-$ or alkyl side chain functionalized plakortolides, together with some diperoxides (that may derive from side chain oxidation of plakortolides) and various side-chain-truncated plakortolides.[2] The study on *P. clathrata* further addressed issues of relative and absolute configuration, in particular revealing that diastereomeric plakortolides, such as plakortolides L (**1**) and K (**2**), uniformly had a 6*S* configuration and thus differed in configuration at the biosynthetically linked C-3 and C-4 centers. This stereochemical situation led to a proposal that the plakortolide biosynthetic pathway in *P. clathrata* involves cyclization of 6-hydroperoxydienoic acid intermediates arising from the stereospecific attachment of a C-6 hydroperoxy group onto a polyketide-derived precursor.[1]

Recently we described an enantiospecific synthesis of the diastereomeric plakortolides E (**3**)[3] and I (**4**)[4] that involved a synthetic route modeling the above proposed plakortolide biosynthetic pathway. The peroxylactone core of the plakortolides was efficiently constructed from (*S*)-2-methylglycidol by diastereoselective Mukaiyama aldol reaction, regioselective hydroperoxidation, and intramolecular hetero-Michael addition onto a butenolide.[5] Plakortolide E (**3**), first reported from the Fijian sponge *Plakortis* sp., has a $Ph(CH_2)_{10}-$ side chain and is a homologue of plakortolide L (**1**). Plakortolide I (**4**), also with a $Ph(CH_2)_{10}-$ side chain, was obtained from the Madagascan *Plakortis* aff. *simplex* by Kashman and co-workers and was characterized by them as the enantiomer of an unnamed plakortolide metabolite (**5**) isolated earlier by the Faulkner research group from a Philippines *Plakinastrella* sp.[6] The published structures of metabolites **4** and **5** are homologues of plakortolide K (**2**) (Figure 1).

In this report, we clarify issues of relative configuration for plakortolide metabolites and thereby establish that the Kashman group likely isolated plakortolide E (**3**) rather than plakortolide I (**4**). We also detail the unreliability of specific rotation measurements in the determination of absolute configuration within the plakortolide class of metabolites.

RESULTS AND DISCUSSION

Relative Configurational Issues. Analysis of the ^1H and ^{13}C NMR values for C-7 and the C-6 methyl substituent of plakortolides, together with relevant NOE data,[1,5] guides the correct determination of their relative configuration. Typical data for plakortolide L (**1**) compared to those of its diastereomer plakortolide K (**2**) are as follows: **1**, C-7 δ_C

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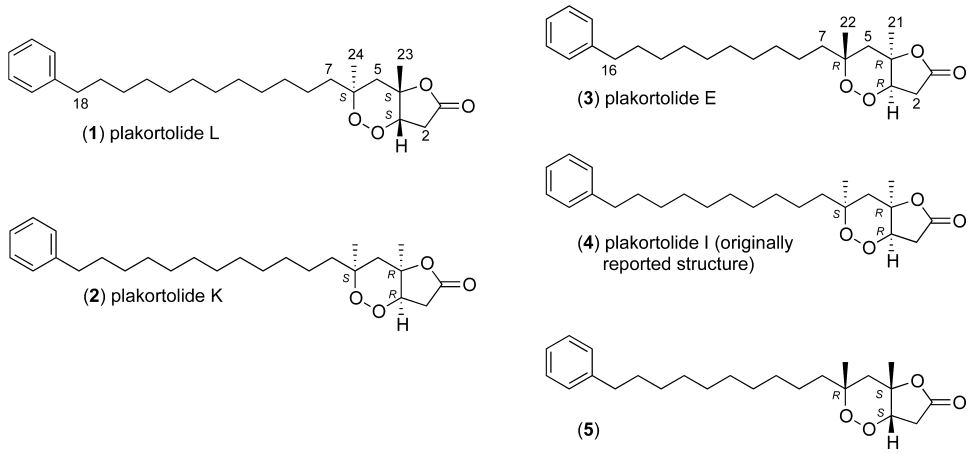

Figure 1. Selected plakortolide metabolites with a $Ph(CH_2)_{12}-$ or $Ph(CH_2)_{10}-$ side chain.

Table 1. Comparison of ^1H and ^{13}C NMR Assignments for Synthetic and Natural Samples of Plakortolides E and I

	synthetic plakortolide E (**3**)		natural plakortolide E (**3**)[a]		synthetic plakortolide I (**4**)		natural plakortolide I (**5**)[b]	
position	δ_C[c]	δ_H (J in Hz)[d]	δ_C[e]	δ_H (J in Hz)[f]	δ_C[c]	δ_H (J in Hz)[d]	δ_C[g]	δ_H (J in Hz)[h]
1	174.2		174.2		174.1		174.1	
2a	34.3	2.92, dd (18.5, 6.1)	34.2	2.91, dd (12.4, 6.0)	34.1	2.90, dd (18.5, 5.9)	34.1	2.91, dd (18.6, 6.0)
2b		2.62, d (18.5)		2.70, d (12.4)		2.56, d (18.5)		2.59, dd (18.6, 1.5)
3	81.1	4.45, d (6.1)	80.1	4.44, d (6.0)	80.8	4.48, d (5.9)	80.8	4.49, d (6.0)
4	82.8		82.0		82.5		82.5	
5a	40.6	2.17, d (14.8)	39.5[i]	2.17, d (15.0)	40.2	2.27, d (15.0)	40.2	2.28, d (15.3)
5b		1.71, d (14.8)		1.71, d (15.0)		1.65, d (15.0)		1.66, d (15.3)
6	80.1		80.2		80.2		80.2	
7	41.0	1.50, m	41.0[i]	1.50, m	36.9	1.52−1.76, m	36.9	1.75, m
8	23.1	1.27, m	23.0[i]	1.25, m	23.7	1.26, m	23.7	1.27−1.30, m
9−14	29.3−30.0	1.27, m	29.5	1.25, m	29.3−29.9	1.26, m	29.3−29.9	1.27−1.30, m
15	31.5	1.61, m	31.4	1.58, m	31.5	1.61, m	31.5	1.57, m
16	36.0	2.60 (t, 7.7)	36.0[i]	2.60 (t, 7.0)	36.0	2.60 (t, 7.8)	36.0	2.60 (t, 7.8)
17	142.9		142.2		143.0		143.0	
18	128.4	7.15−7.29 (m)	128.3	7.20−7.25 (m)	128.4	7.15−7.29 (m)	128.4	7.19, m
19	128.2	7.15−7.29 (m)	128.2	7.20−7.25 (m)	128.2	7.15−7.29 (m)	128.2	7.27, m
20	125.5	7.15−7.29 (m)	125.5	7.20−7.25 (m)	125.5	7.15−7.29 (m)	125.5	7.19, m
21	25.9	1.39, s	25.8	1.37, s	25.9	1.37, s	25.9	1.38, s
22	22.4	1.29, s	22.4[i]	1.27, s	24.8	1.20, s	24.9	1.20, s

[a]Data from ref 4; revised structure (see text); sample originally named as plakortolide I. [b]Data from ref 6. [c]100 MHz; chemical shifts (ppm) referenced to $CDCl_3$ (δ_C 77.16). [d]400 MHz; chemical shifts (ppm) referenced to $CHCl_3$ (δ_H 7.26). [e]100 MHz; chemical shifts (ppm) referenced to $CDCl_3$ (δ_C 77.0). [f]500 MHz; chemical shifts (ppm) referenced to TMS. [g]100 MHz; reference not stated. [h]300 MHz; reference not stated. [i]Revised assignments (see text for details).

40.8; C-24, δ_H 1.27; δ_C 22.2 vs **2**, C-7 δ_C 36.6; C-24, δ_H 1.18; δ_C 24.4. Additionally, the diastereotopic H-5 signals are diagnostic: for **1**, δ_H 2.15 and 1.68 vs **2**, δ_H 2.25 and 1.63.[1] Against this background, when the literature data[4] for the structure **4** named as "plakortolide I" were examined, some inconsistencies became apparent. In the ^1H NMR data, the chemical shift values of the C-5 protons (δ_H 2.17 and 1.71) and of Me-22 (δ_H 1.27) were all more consistent with a *trans* arrangement of the C-4 and C-6 Me groups than with the published *cis* arrangement. On first inspection, the ^{13}C NMR data appeared to match the proposed structure (C-7 δ_C 36.0), but on closer inspection, the published value (δ_C 39.5) for the benzylic C-16 appeared incorrect. The chemical shift value for this carbon is generally ~36.0 ppm.[1] The NMR assignments of synthetic samples of diastereomers **3** and **4** were examined by HSQC analysis, and the following assignments were confirmed: **3**, δ_C 40.6 (C-5); δ_C 41.0 (C-7); δ_C 36.0 (C-16); δ_C 22.4 (Me-22); and **4**, δ_C 40.2 (C-5); δ_C 36.9 (C-7); δ_C 36.0 (C-16); δ_C 24.8 (Me-22). Against this background, we reviewed the assignments for the "plakortolide I" sample isolated by the Kashman group and suggest that the signals originally assigned to C-5 (δ_C 41.0), C-7 (δ_C 36.0), and C-16 (δ_C 39.5) should be revised to C-5 (δ_C 39.5), C-7 (δ_C 41.0), and C-16 (δ_C 36.0). Furthermore, we suggest that the chemical shift values originally assigned to C-8 (δ_C 22.4) and Me-22 (δ_C 23.0) should be revised to C-8 (δ_C 23.0) and Me-22 (δ_C 22.4) so that the assignment for Me-22 is consistent with typical values for a plakortolide structure.[1] With these proposed changes, as shown in Table 1, the ^1H and ^{13}C NMR data reported by Kashman and co-workers[4] matched well those of synthetic plakortolide E[5] except for the geminal coupling constant reported for H-2 and for small discrepancies (<1 ppm) in the values for C-3, C-4, and C-5.[7] The revised ^{13}C NMR assignments now also implied that the C-4Me/C-6Me groups in "plakortolide I" are in a *trans* rather than a *cis*

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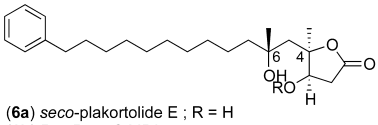
Table 2. Revised Structures and Names of Selected Plakortolide Metabolites

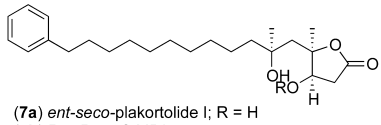
original structure	published configuration	new structure or name	revised configuration	comments
plakortolide E (**3**)	3*R*, 4*R*, 6*R*	*seco*-plakortolide E (**6a**)	unchanged	
plakortolide I (**4**)	3*R*, 4*R*, 6*S*	plakortolide E (**3**)	3*R*, 4*R*, 6*R*	structure **4** named as
unnamed plakortolide (**5**)	3*S*, 4*S*, 6*R*	plakortolide I (**5**)	unchanged	*ent*-plakortolide I

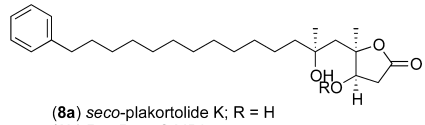
Table 3. Comparison of MPA and MTPA Ester Data for Synthetic *seco*-Plakortolide E and the *seco* Derivative of *ent*-Plakortolide I with Those of Equivalent Esters Prepared from *seco* Derivatives of Natural Plakortolides E, I, K, and L

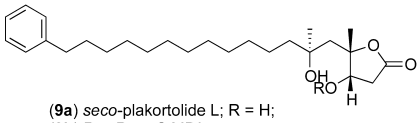
	seco-plakortolide E (synthetic) (**6a**)[5]		*ent-seco*-plakortolide I (synthetic) (**7a**)		*seco*-plakortolide K (**8a**)[1]	*seco*-plakortolide L (**9a**)[1]	*seco*-plakortolide E (**6a**)[3,a]	*seco*-plakortolide I **11a**[6]
position	$\Delta\delta_{RS}$ MPA **6b**	$\Delta\delta_{SR}$ MTPA **6c**	$\Delta\delta_{RS}$ MPA **7b**	$\Delta\delta_{SR}$ MTPA **7c**	$\Delta\delta_{RS}$ MPA **8b**	$\Delta\delta_{RS}$ MPA **9b**	$\Delta\delta_{RS}$ MPA **10**	$\Delta\delta_{SR}$MTPA **11b**
H2	0.09	0.02	0.09	0.02	0.09	−0.08	0.10	−0.023
H2′	0.23	0.08	0.25	0.08	0.25	−0.22	0.10	−0.0005
C-4 Me	−0.06	−0.03	−0.04	−0.02	−0.04	0.05	[b]	0.026
H5	−0.34	−0.14	−0.33	−0.12	−0.33	0.36	[b]	0.122
H5′	−0.37	−0.08	−0.39	−0.10	−0.39	0.33	[b]	0.106
C-6 Me	−0.31	−0.17	−0.16	−0.07	−0.16	0.29	[b]	0.061

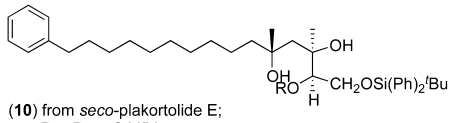
[a]MPA ester of a TBDPS-protected tetraol prepared from the natural product by $LiAlH_4$ reduction. [b]Chemical shift data not provided in ref 3.


(**6a**) *seco*-plakortolide E ; R = H
(**6b**) R = *R*- or *S*-MPA
(**6c**) R = *R*- or *S*-MTPA

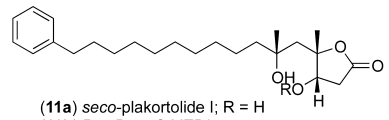

(**7a**) *ent-seco*-plakortolide I; R = H
(**7b**) R = *R*- or *S*-MPA
(**7c**) R = *R*- or *S*-MTPA


(**8a**) *seco*-plakortolide K; R = H
(**8b**) R = *R*- or *S*-MPA


(**9a**) *seco*-plakortolide L; R = H;
(**9b**) R = *R*- or *S*-MPA



(**10**) from *seco*-plakortolide E;
R = *R*- or *S*-MPA


(**11a**) *seco*-plakortolide I; R = H
(**11b**) R = *R*- or *S*-MTPA

arrangement. Consequently, the structure of the Kashman isolate most likely corresponds to that of plakortolide E (**3**).

The erroneous stereochemical determination published by the Kashman group may have been compromised since the spectroscopic data originally attributed to plakortolide E (**3**) did not match the structure proposed.[3] In our own structural work, a comparison of NMR data for synthetic *seco* diols prepared by Zn/AcOH reduction of plakortolides K (**2**) and L (**1**) with relevant literature data led us to conclude that the NMR data published for plakortolide E (**3**) were in fact those of the *seco* diol (**6a**).[1] The subsequent synthesis of both plakortolide E (**3**) and *seco*-plakortolide E (**6a**) further confirmed that incorrect chemical shift data had originally been provided for plakortolide E (**3**).[5]

A clarification in nomenclature is required. Owing to the apparent correction of absolute configuration for "plakortolide I" in the synthetic study,[5] stereoisomer **4** was named *ent*-plakortolide I rather than plakortolide I. The enantiomer **5**, previously unnamed, can therefore be named plakortolide I. This is preferable to the previous name of 6-epiplakortolide E given to **5** by Jung et al. in a paper describing the synthesis of racemic **5**,[8] because the latter name is misleading. Both **3**[3] and **5**[6] have been shown by Mosher ester analysis to possess a 6*R* configuration, and so these two metabolites cannot be C-6 epimers. For reference, the ^1H and ^{13}C NMR data of synthetic *ent*-plakortolide I (**4**) and of natural plakortolide I (**5**) are shown in Table 1 alongside the data of natural and synthetic plakortolide E (**3**). Table 2 summarizes the changes in nomenclature that we recommend.

Clarification of Absolute Configuration of Plakortolides. Synthetic samples of plakortolide E (**3**), with a (3*R*,4*R*,6*R*) configuration, and *ent*-plakortolide I (**4**), with a (3*R*,4*R*,6*S*) configuration, have $[\alpha]_D$ values of +14.9 (*c* 0.76, $CHCl_3$) and −9 (*c* 0.7, $CHCl_3$), respectively.[5] Synthetic samples of *seco*-plakortolide E (**6a**), of (3*R*,4*R*,6*R*) configuration,[3] and the *ent* isomer of *seco*-plakortolide I (**7a**), of (3*R*,4*R*,6*S*) configuration, have $[\alpha]_D$ values of +6.9 (*c* 0.15, $CHCl_3$)[9] and +9.8 (*c* 0.27, $CHCl_3$), respectively

When compared to these reference values, the specific rotation values published for some plakortolide metabolites appear inconsistent. Plakortolide I (**5**), with a reported $[\alpha]_D$ −8 (*c* 0.05, $CHCl_3$), was deduced to have a 3*S* configuration from MPA ester analysis.[6] However, since the synthetic sample of *ent*-plakortolide I (**4**), with a 3*R* configuration, has a negative rotation, the specific rotation for **5** should have been positive. Plakortolide K (**2**), with a reported $[\alpha]_D$ +8.8 (*c* 0.03, $CHCl_3$), was deduced to have a 3*R* configuration from MPA ester analysis.[1] However, in view of the sign of rotation of *ent*-plakortolide I (**4**), a negative rotation would have been expected for **2**. It is generally accepted that chiral homologues should possess the same sign of optical rotation, although there are exceptions to this rule.[10] Noting that the various measurements were made at different concentrations and on different instruments, the optical rotation of synthetic **4** was recorded at a lower concentration, giving an averaged $[\alpha]_D$ −11 (*c* 0.04, $CHCl_3$), and with a range of specific rotations that varied between −13 and −8. For comparison, the individual $[\alpha]_D$ values for the plakortolide K (**2**) sample ranged between

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+20 and −1, resulting in the averaged value of +8.8 that was reported. A further sample of plakortolide K (**2**) was next isolated from sponge crude extract and gave $[\alpha]_D$ values from −8 to −14 (*c* 0.04, $CHCl_3$), leading to an averaged value of −11, which agreed with that of the synthetic sample of the homologue *ent*-plakortolide I. The specific rotation data for the *seco* derivatives of **2** and **4** were also compared. *seco*-Plakortolide K (**8a**) prepared from natural material had $[\alpha]_D$ +13.5 (*c* 0.04, $CHCl_3$) and with the range of individual measurements between +11 and +16, compared to +9.8 (*c* 0.27, $CHCl_3$) for the *seco* derivative of synthetic *ent*-plakortolide I (**7a**). There was also better agreement when data for plakortolide L (**1**) were compared with those of plakortolide E (**3**). Plakortolide L (**1**), with an $[\alpha]_D$ −4.6 (*c* 0.16, $CHCl_3$) averaged across individual values that ranged from −9.6 to −1.5 and a 3*S* configuration from MPA ester analysis,[1] had the opposite sign of rotation compared to synthetic **3**, of 3*R* configuration. *seco*-Plakortolide L (**9a**) prepared from natural material had $[\alpha]_D$ −11.0 (*c* 0.04, $CHCl_3$) compared to +6.9 (*c* 0.15, $CHCl_3$)[9] for the *seco* derivative (**6a**) of synthetic plakortolide E.

Although, understandably, the experimental error associated with the measurement of dilute samples is significant, we wished to be sure that this was the source of the error. An alternative explanation for the inconsistencies was that the various MPA or MTPA analyses were somehow misleading.[11] MPA esters **6b** and **7b** were therefore prepared from synthetic samples of *seco*-plakortolide E (**6a**) and the *seco* derivative of *ent*-plakortolide I (**7a**), respectively, and their NMR data compared with those of the equivalent esters[1,3] prepared from natural plakortolides (Table 3). First, comparison of the MPA esters **9b** obtained from *seco*-plakortolide L (**9a**)[1] with MPA esters **6b** confirmed that natural (−)-plakortolide L (**1**) and synthetic (+)-plakortolide E (**3**) have opposite configurations (**1** 3*S*, 4*S*, 6*S*; **3** 3*R*, 4*R*, 6*R*). Analysis of the MPA esters (**10**) prepared earlier from a derivative of (+)-*seco*-plakortolide E by Varoglu et al. had also yielded a 3*R* configuration, although it should be noted that their report contained limited NMR data.[3] These various experiments all support a consistency between optical rotation data and Mosher ester results in plakortolides with a *trans* arrangement of the C-4 and C-6 methyl groups. On the basis of the reported specific rotation of +8 (*c* 0.0173, $CHCl_3$),[4] and subject to the caveat explored above, it seems likely that the Kashman group may have isolated (3*R*,4*R*,6*R*)-plakortolide E (**3**) from *Plakortis* aff. *simplex*.

In contrast, MPA esters **7b** and **8b**, prepared from synthetic (−)-*ent*-plakortolide I (**4**)[5] and natural plakortolide K (**2**),[1] respectively, were each assigned a (3*R*, 4*R*, 6*S*) configuration, despite the positive specific rotation originally reported for **2**. Furthermore, comparison of the NMR data for MTPA esters (**7c**) of **4** with the literature data for MTPA esters (**11**) derived from plakortolide I (**5**)[6] revealed an enantiomeric relationship (**4** 3*R*, 4*R*, 6*S*; **5** 3*S*, 4*S*, 6*R*), despite both **4** and **5** showing a negative specific rotation. These data clearly establish the inadvisability of using specific rotation data measured at the sodium D wavelength to establish absolute configuration in plakortolides for which there is a *cis* arrangement of the C-4 and C-6 methyl groups.

We have previously commented[1] that "the small magnitude of $[\alpha]_D$ values associated with many of the plakortolide metabolites isolated suggests that it would be speculative to assign either absolute or relative configuration on the basis of $[\alpha]_D$ values alone." Stereochemical determinations for complex natural products that involve a comparison with the data for candidate synthetic stereoisomers can easily be compromised by the experimental and instrumental errors inherent in optical rotation measurements, by variations in temperature, solvent, or concentration,[12] or by the presence of chiral impurities,[13] each of which may impact on small rotation values. Rigid molecules, for example 5-substituted-2(5*H*)-furanones of the same absolute configuration, have been shown to exhibit specific rotations of opposite sign.[10] In the case of conformationally flexible molecules, the equilibrium population of the various conformers generates a conformationally averaged $[\alpha]_D$ value.[14] For example, the marine alkaloids haliclonacyclamines A and B, with small $[\alpha]_D$ values that are opposite in sign, were assigned the same absolute configuration by X-ray crystallography using Cu Kα radiation. These two alkaloids differed in conformation solely as a consequence of different double-bond positioning in the methylene chains connected to the bipiperidine core.[15] Low-temperature NMR studies (to be reported in detail elsewhere) have confirmed the conformational flexibility of the peroxylactone moiety in plakortolides.

■ CONCLUSIONS

The structure of a plakortolide metabolite isolated from *Plakortis* aff. *simplex* and named "plakortolide I" is revised to that of plakortolide E, likely of (3*R*,4*R*,6*R*) configuration. We suggest that the plakortolide I name can be retained for the stereoisomeric metabolite **5** isolated earlier by the Faulkner group from a Philippino *Plakinastrella* sp. Specific rotation data should be used with caution to determine the absolute configuration of plakortolides, notably in those cases where there is a *cis* configuration for the C-4 and C-6 methyl groups. Instead, analysis of NMR data for MPA or MTPA ester derivatives leads to a reliable determination of the absolute configuration. Such comparisons were used to verify that the absolute configurations of plakortolides K (**2**) and I (**5**) are (3*R*, 4*R*, 6*S*) and (3*S*, 4*S*, 6*R*), respectively, while those of plakortolides L (**1**) and E (**3**) are (3*S*, 4*S*, 6*S*) and (3*R*, 4*R*, 6*R*), respectively.

■ EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were obtained using a JASCO P-2000 polarimeter (U. Qld) or a Perkin-Elmer 343 polarimeter (U. Lyon) for solutions in $CHCl_3$. NMR spectra were recorded at ambient probe temperature on a Bruker AV 500 spectrometer unless otherwise stated. ^{1}H NMR spectra were referenced to the residual solvent peak at δ = 7.26 ($CHCl_3$). ^{13}C NMR spectra were referenced to the solvent peak at δ = 77.16 ($CDCl_3$). HRMS analyses were conducted using a Thermofinigan MAT 95 XL instrument. Reagents and solvents were purified by standard means. DCM was distilled from CaH_2. Analytical TLC was performed on Merck silica gel 60 F254 plates. Flash chromatography was performed on silica gel (230−400 mesh) purchased from Macherey Nagel. PTLC was performed on Silicycle plates (F-254, 1000 μm).

***Seco* Derivative of *ent*-Plakortolide I (7a).** To a solution of *ent*-plakortolide I (**4**) (6.3 mg, 0.016 mmol) in anhydrous Et_2O (2 mL) were added HOAc (709 μL, 80 equiv) and Zn (42 mg, 4 equiv). The mixture was stirred for 24 h, filtered, and evaporated to give the *seco* derivative of *ent*-plakortolide I (**7a**) (6.2 mg, 98% yield): $[\alpha]^{20}_D$ +9.8 (*c* 0.27, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.29−7.26 (2H, m), 7.18−7.15 (3H, m), 4.24 (1H, d, *J* = 5.9 Hz), 2.91 (1H, dd, *J* = 18.1, 6.0 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.53 (1H, d, *J* = 18.1 Hz), 2.38 (1H, d, *J* = 14.7 Hz), 1.88 (1H, d, *J* = 14.7 Hz), 1.64−1.52 (4H, m), 1.47 (3H, s), 1.36 (3H, s), 1.27 (14H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 175.2, 143.1, 128.5, 128.4, 125.7, 90.6, 73.6, 72.9, 46.7, 44.2, 37.9,

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36.1, 31.7, 30.0, 29.7 (3C), 29.6, 29.5, 28.5, 26.2, 24.1; HR-ESIMS *m/z* 413.2662 $[M + Na]^+$ (calculated for $C_{24}H_{38}NaO_4$ 413.2650).

Procedure for the Preparation of MPA or MTPA Esters. The *seco* derivatives (**6a**, **7a**) of plakortolide E (**3**)[5] or *ent*-plakortolide I (**4**) (1 mg, 2.56 μmol, 1 equiv) were individually treated with MPA (2.1 mg, 12.8 μmol, 5 equiv) or MTPA (3 mg, 12.8 μmol, 5 equiv) followed by DCC (2.6 mg, 12.8 μmol, 5 equiv) and DMAP (1.6 mg, 12.8 μmol, 5 equiv) in dry DCM (0.6 mL). Each reaction was stirred for 1−2 h, filtered through a small pad of silica gel, concentrated to 0.2 mL, and chromatographed on preparative TLC (Et_2O).

(*R*)-(2*R*,3*R*)-2-[(*R*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 2-Methoxy-2-phenylacetate. The (*R*)-MPA derivative of *seco*-plakortolide E (0.9 mg, 66%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44−7.35 (5H, m), 7.29−7.26 (2H, m), 7.19−7.16 (3H, m), 5.21 (1H, dd, *J* = 6.0, 1.1 Hz), 4.76 (1H, s), 3.38 (3H, s), 3.05 (1H, dd, *J* = 18.6, 6.1 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.50 (1H, dd, *J* = 18.5, 1.2 Hz), 1.59 (1H, d, *J* = 15.2 Hz), 1.66−1.53 (4H, m), 1.49 (3H, s), 1.41 (1H, d, *J* = 15.2 Hz), 1.37−1.22 (14H, m), 0.84 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 173.4, 169.5, 143.1, 135.6, 129.5, 129.2, 128.5, 128.4, 127.7, 125.7, 88.4, 82.4, 76.3, 72.1, 57.3, 43.4, 43.0, 36.1, 36.0, 31.7, 30.2, 29.80, 29.78, 29.74, 29.68, 29.5, 28.4, 24.8, 24.0; HR-ESIMS *m/z* 561.3172 $[M + Na]^+$ (calculated for $C_{33}H_{46}NaO_6$ 561.3187).

(*S*)-(2*R*,3*R*)-2-[(*R*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 2-Methoxy-2-phenylacetate. The (*S*)-MPA derivative of *seco*-plakortolide E (0.9 mg, 68%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.42−7.35 (5H, m), 7.29−7.26 (2H, m), 7.18−7.16 (3H, m), 5.21 (1H, dd, *J* = 6.3, 1.6 Hz), 4.81 (1H, s), 3.41 (3H, s), 2.96 (1H, dd, *J* = 18.5, 6.4 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.27 (1H, dd, *J* = 18.6, 1.6 Hz), 1.93 (1H, d, *J* = 15.1 Hz), 1.78 (1H, d, *J* = 15.0 Hz), 1.64−1.47 (4H, m), 1.55 (3H, s), 1.37−1.24 (14H, m), 1.15 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 173.2, 169.8, 143.1, 135.4, 129.3, 129.1, 128.5, 128.4, 127.0, 125.7, 88.1, 82.6, 76.4, 72.3, 57.6, 44.1, 43.4, 36.1, 35.6, 31.7, 30.2, 29.81, 29.77, 29.73, 29.67, 29.5, 28.8, 25.2, 24.3; HR-ESIMS *m/z* 561.3177 $[M + Na]^+$ (calculated for $C_{33}H_{46}NaO_6$ 561.3187).

(*R*)-(2*R*,3*R*)-2-[(*R*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. The (*R*)-MTPA derivative of *seco*-plakortolide E (0.63 mg, 39%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.50−7.42 (5H, m), 7.29−7.26 (2H, m), 7.18−7.15 (3H, m), 5.30 (1H, dd, *J* = 6.3, 2.1 Hz), 3.46 (3H, m), 3.10 (1H, dd, *J* = 18.6, 6.4 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.49 (1H, dd, *J* = 18.6, 2.1 Hz), 1.95 (1H, d, *J* = 15.2 Hz), 1.75 (1H, d, *J* = 15.2 Hz), 1.60 (3H, s), 1.64−1.20 (18H, m), 1.14 (3H, s); HR-ESIMS *m/z* 629.3057 $[M + Na]^+$ (calculated for $C_{34}H_{45}F_3NaO_6$ 629.3060).

(*S*)-(2*R*,3*R*)-2-[(*R*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. The (*S*)-MTPA derivative of *seco*-plakortolide E (0.68 mg, 42%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.54−7.40 (5H, m), 7.29−7.26 (2H, m), 7.18−7.15 (3H, m), 5.30 (1H, dd, *J* = 6.2, 1.9 Hz), 3.56 (3H, m), 3.12 (1H, dd, *J* = 18.6, 6.2 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.57 (1H, dd, *J* = 18.7, 1.9 Hz), 1.81 (1H, d, *J* = 15.1 Hz), 1.67 (1H, d, *J* = 15.2 Hz), 1.57 (3H, s), 1.64−1.20 (18H, m), 0.97 (3H, s); HR-ESIMS *m/z* 629.3051 $[M + Na]^+$ (calculated for $C_{34}H_{45}F_3NaO_6$ 629.3060).

(*R*)-(2*R*,3*R*)-2-[(*S*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 2-Methoxy-2-phenylacetate. The (*R*)-MPA derivative of *ent-seco*-plakortolide I (0.9 mg, 63%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.44−7.35 (5H, m), 7.29−7.26 (2H, m), 7.19−7.16 (3H, m), 5.21 (1H, d, *J* = 5.2 Hz), 4.76 (1H, s), 3.38 (3H, s), 3.05 (1H, dd, *J* = 18.6, 6.1 Hz), 2.61 (2H, t, *J* = 7.8 Hz), 2.49 (1H, d, *J* = 19.3 Hz), 1.51 (1H, d, *J* = 14.8 Hz), 1.51 (3H, s), 1.68−1.22 (18H, m), 1.41 (1H, d, *J* = 15.2 Hz), 1.12 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 173.6, 169.5, 143.1, 135.7, 129.5, 129.2, 128.5, 128.4, 127.6, 125.7, 88.4, 82.5, 76.6, 72.2, 57.3, 45.4, 43.5, 36.1, 35.9, 31.7, 30.2, 29.80, 29.76, 29.68, 29.5, 27.2, 24.8, 24.3, 23.7; HR-ESIMS *m/z* 561.3166 $[M + Na]^+$ (calculated for $C_{33}H_{46}NaO_6$ 561.3187).

(*S*)-(2*R*,3*R*)-2-[(*S*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 2-Methoxy-2-phenylacetate. The (*S*)-MPA derivative of *ent-seco*-plakortolide I (1 mg, 68%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.43−7.34 (5H, m), 7.29−7.26 (2H, m), 7.18−7.15 (3H, m), 5.23 (1H, dd, *J* = 6.3, 1.4 Hz), 4.80 (1H, s), 3.41 (3H, s), 2.96 (1H, dd, *J* = 18.5, 6.3 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.24 (1H, dd, *J* = 18.5, 1.5 Hz), 1.84 (1H, d, *J* = 15.0 Hz), 1.80 (1H, d, *J* = 15.0 Hz), 1.56 (3H, s), 1.63−1.24 (18H, m), 1.28 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 173.5, 169.8, 143.1, 135.5, 129.3, 129.0, 128.5, 128.4, 127.1, 125.7, 88.2, 82.7, 76.6, 72.4, 57.6, 45.9, 43.6, 36.1, 35.5, 31.7, 30.3, 29.80, 29.78, 29.73, 29.67, 29.5, 27.9, 25.0, 23.9; HR-ESIMS *m/z* 561.3165 $[M + Na]^+$ (calculated for $C_{33}H_{46}NaO_6$ 561.3187).

(*R*)-(2*R*,3*R*)-2-[(*S*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. The (*R*)-MTPA derivative of *ent-seco*-plakortolide I (0.5 mg, 30%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.50−7.41 (5H, m), 7.29−7.26 (2H, m), 7.18−7.15 (3H, m), 5.31 (1H, dd, *J* = 6.2, 1.7 Hz), 3.46 (3H, m), 3.11 (1H, dd, *J* = 18.7, 6.2 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.47 (1H, dd, *J* = 18.6, 1.7 Hz), 1.86 (1H, d, *J* = 15.1 Hz), 1.77 (1H, d, *J* = 15.1 Hz), 1.61 (3H, s), 1.62−1.20 (18H, m), 1.27 (3H, s); HR-ESIMS *m/z* 629.3045 $[M + Na]^+$ (calculated for $C_{34}H_{45}F_3NaO_6$ 629.3060).

(*S*)-(2*R*,3*R*)-2-[(*S*)-2-Hydroxy-2-methyl-12-phenyldodecyl]-2-methyl-5-oxotetrahydrofuran-3-yl 3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate. The (*S*)-MTPA derivative of *ent-seco*-plakortolide I (0.5 mg, 30%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.52−7.40 (5H, m), 7.30−7.26 (2H, m), 7.19−7.15 (3H, m), 5.30 (1H, dd, *J* = 6.1, 1.4 Hz), 3.56 (3H, m), 3.13 (1H, dd, *J* = 18.7, 6.1 Hz), 2.60 (2H, t, *J* = 7.8 Hz), 2.55 (1H, dd, *J* = 18.7, 1.4 Hz), 1.74 (1H, d, *J* = 15.0 Hz), 1.67 (1H, d, *J* = 15.1 Hz), 1.59 (3H, s), 1.64−1.21 (18H, m), 1.20 (3H, s); HR-ESIMS *m/z* 629.3038 $[M + Na]^+$ (calculated for $C_{34}H_{45}F_3NaO_6$ 629.3060).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures S1−S23. ^{1}H and selected 2D NMR data for compounds **3**, **4**, **6a−c**, and **7a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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