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Synthesis of the Sponge-Derived Plakortone Series of Bioactive Compounds

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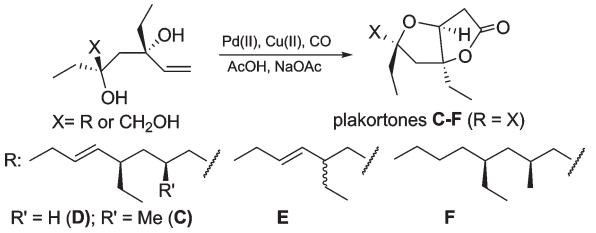

The Caribbean sponges of the genus *Plakortis*, *P. halichondrioides*, and *P. simplex* have provided a series of biologically active furanolactones—the plakortones A−D (**1**−**4**) from the former sponge and B−F (**2**−**6**) from the latter. The defining motif of the plakortones is a sterically congested 2,6-dioxabicyclo[3.3.0]octan-3-one moiety, the emblematic furanolactone core. This core is efficiently accessed by a palladium(II) mediated hydroxycyclization−carbonylation−lactonization cascade with an appropriate ene-1,3-diol. Total syntheses of plakortones C (**3**) and F (**6**) are now described which settle constitutional and stereochemical features in this group of secondary metabolites. Acquisition of plakortone D (**4**), the most effective activator of SR-Ca^{2+}-pumping ATPase, utilized stereodefined lactone cores that resulted from asymmetric dihydroxylation of protected homoallylic alcohol **29**. A derived lactone aldehyde was then coupled with an independently generated, sulfone-activated side chain unit, **57**. The 11,12-*E*-double bond, carried through the sequence as a protected, stereodefined diol, was released therefrom by stereospecific *syn*-elimination via an orthoester derivative. In this way, plakortone D (**4**) was demonstrated to possess the (3*S*,4*S*,6*S*,10*R*,11*E*) configuration. Racemic plakortone E (**5**) was also acquired by using the Pd(II) induced sequence, but in this case, the required, complete acyclic system **52** was assembled first. Plakortone C (**3**) resulted from a sequence commencing with (*R*)-(+)-3-hydroxy-2-methylpropionate, with a derived iodide **76** alkylating the enolate of the butyramide **77** generated from (1*S*,2*S*)-(+)-pseudoephedrine. The liberated primary alcohol **79** was converted by standard procedures to key enediol **89** which, with the Pd(II) protocol, afforded the major separable plakortones **90** and **91**, with the former being identical with natural plakortone C (**3**). Very mild hydrogenation of **90** afforded a saturated plakortone, identical with natural plakortone F (**6**), thus establishing its structure and absolute stereochemistry. Available information on the stereoselective routes to plakortones E (**5**) and B (**2**) are also outlined, so that the constitution and absolute stereochemistry of plakortones B−F are now established.

Introduction

Sponges of the genus *Plakortis* are adept in the production of biologically active secondary metabolites, among which peroxides and lactones are especially prominent.[1] The Caribbean species *P. halichondrioides* and *P. simplex* are prolific in this regard, and have provided a fascinating series

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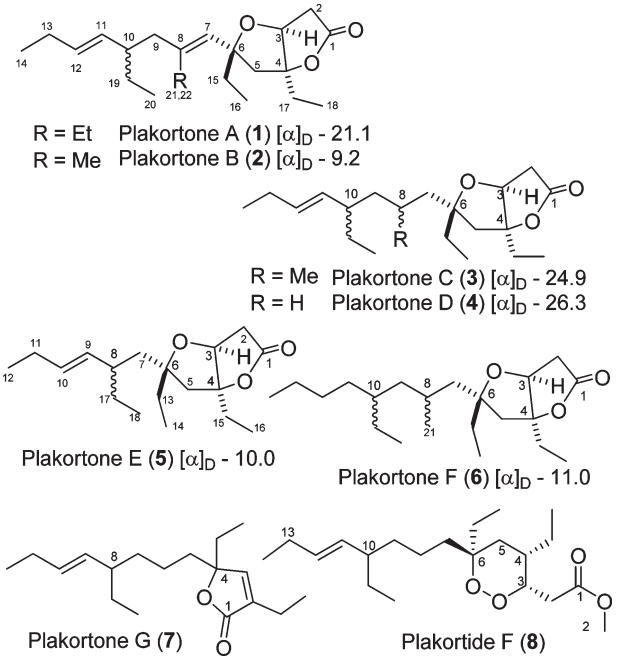


FIGURE 1. Structures of plakortones A−G (**1**−**7**) and plakortide F (**8**).

of furanolactones—the plakortones A−F (**1**−**6**),[2−4] with A−D (**1**−**4**)[2] from the former sponge and B−F (**2**−**6**)[3] from the latter. Plakortone G (**7**),[5] from the Jamaican sponge *Plakortis* sp., is simpler in structure, probably biosynthetically related to the peroxide, plakortide F (**8**),[6] and stereochemically relevant to the plakortones A−F (**1**−**6**).

Plakortones A−D (**1**−**4**) constitute a new group of activators of the cardiac SR-Ca^{2+}-pumping ATPase and are of interest with respect to correction of cardiac muscle relaxation irregularities. Plakortone D (**4**) is the most active in this connection and overall the plakortones represent a new family of pharmacological importance. The structures deduced by Patil and co-workers,[2] and subsequently by Fattorusso,[3] are portrayed in Figure 1 with the partial relative stereochemistry based on NOE difference data. The absolute stereochemistry was not determined for any of the plakortone congeners.

The pharmacological properties associated with these unusual metabolites generated interest in their synthesis and our acquisition of plakortone D (**4**)[7] confirmed its constitution and established its absolute stereochemistry (Figure 2).

These strategies then guided us to plakortones E (**5**),[8] C (**3**), and F (**6**), and established the absolute stereochemistry of the latter two. Others have subsequently reported syntheses of plakortones E (**5**)[9] and B (**2**).[10] We now report in full our syntheses of plakortones D (**4**),[7] C (**3**), and F (**6**), which along with data for plakortones E (**5**)[9] and B (**2**),[10] provide

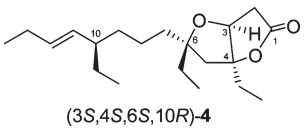


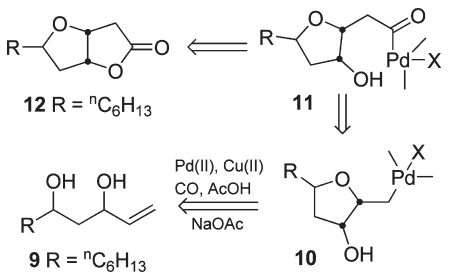
FIGURE 2. Structure and absolute stereochemistry of plakortone D (**4**).

constitutional and stereochemical definition for the known plakortone congeners.

General Approach

Early contributions[11−14] focused on construction of the emblematic structural motif of the plakortones viz. the 2,6-dioxabicyclo[3.3.0]octan-3-one, a *cis*-fused tetrahydrofuranolactone moiety. We considered an economical and flexible route might be based on metal ion induced ring closure of a suitable hydroxy alkene that would deliver the tetrahydrofuran unit, bearing a pendant primary carbon−metal bond. Carbonylation, well-known for Pd(II) systems, would provide the additional carbon at the appropriate oxidation level and then intramolecular lactonization, with formal expulsion of (reoxidizable) Pd(0), would consummate the sequence. This retrosynthesis is shown below in Scheme 1. Early work of Semmelhack[15] and later reports by Jäger[16] with carbohydrate-based enepolyols indicated that ene-1,3-diols would respond to these conditions, and some stereochemical aspects of this transformation were established by Yoshida.[17] The practicality of this "one-pot" conversion of appropriate enediols was demonstrated by our synthesis of the novel bicyclic lactones present in the Hagen's glands of certain parasitic wasps.[18]

SCHEME 1. Likely Component Steps of the Pd(II)-Cascade



Importantly, the sterically congested furanolactone moiety of the plakortones is also efficiently accessed by this Pd(II)-mediated cascade, and furthermore it was tolerant of the additional

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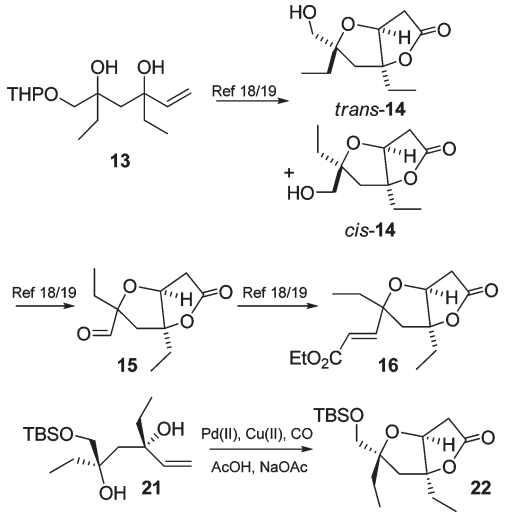
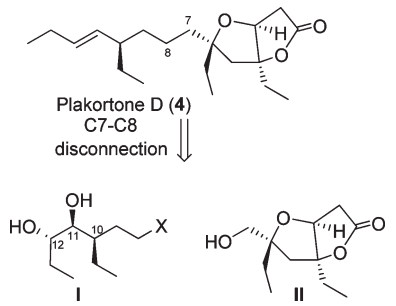
(18) (a) Paddon-Jones, G. C.; Moore, C. J.; Brecknell, D. J.; König, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3479. (b) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; König, W. A.; Kitching, W. *J. Org. Chem.* **2001**, *66*, 7487.

SCHEME 2. Synthesis of Functionalized Plakortone Cores



SCHEME 3. Retrosynthesis of Plakortone D (4)



functionality necessary for strategic chain extension as shown in Scheme 2.[12,19] (For convenience, *trans* and *cis* refer throughout to the orientation of the ethyl groups at C4 and C6 on the tetrahydrofuran ring.)

Results and Discussion: Synthesis of Plakortone Congeners

Plakortone D. Because of its bioactivity, plakortone D (**4**)[2] was targeted initially and its synthesis navigated us to plakortones E (**5**), C (**3**), and F (**6**). The chemistry summarized in Scheme 2 led to the disconnection that unveils the accessible lactone **II** and the side chain moiety **I**.[7] The latter would require stereocontrol at C10, and incorporate a C11−C12 *E*-double bond or a precursor to it (Scheme 3).

Bicyclic Lactone Core. The relative stereochemistry around the lactone core of the plakortones has been settled,[2,3] but not the relationship with side-chain centers, for example at C10 in plakortone D (**4**). Regarding the likely enantiomeric system for synthetic pursuit, some guidance emerges from our review of the *Plakortis* metabolites.[1] The plakortones A−F (**1**−**6**) are all levo-rotatory and assuming that the furanolactone moiety predominately regulates the molecular rotation[20] and remembering that in simpler lactone series, levo-enantiomers manifest the sense of chirality shown below in Figure 3, then our initial quest was for arrangement *trans*-**25**.

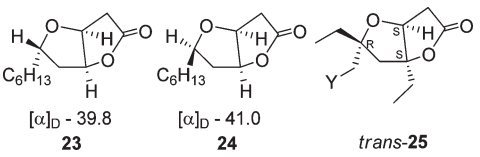
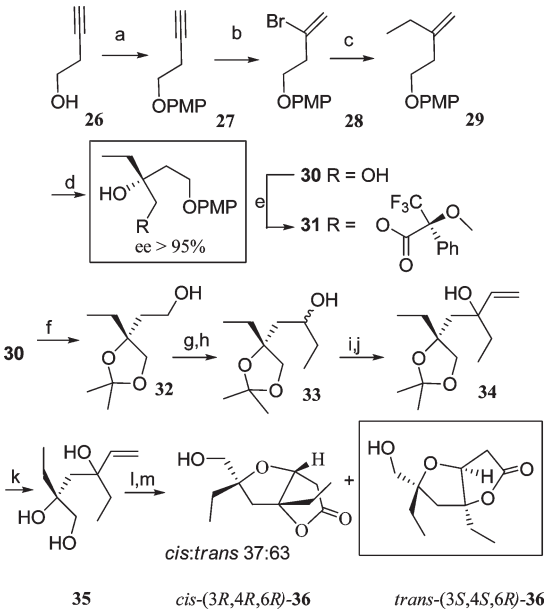


FIGURE 3. The naturally occurring bicyclic lactones **23** and **24**[18b] and *trans*-**25**.

SCHEME 4. Synthesis of Bicyclic Lactones *cis*-(3*R*,4*R*,6*R*)-36 and *trans*-(3*S*,4*S*,6*R*)-36[a]



[a]Reagents and conditions: (a) DEAD, PPh_3, 4-methoxyphenol, 60%; (b) bromo-9-BBN, CH_2Cl_2, rt, 1 h, 68%; (c) EtMgBr, 3% $Fe(acac)_3$, THF-NMP, −5 °C, 15 min, 84%; (d) AD mix β, H_2O, *t*BuOH, 0 °C, 24 h, 81%; (e) (*S*)-Mosher acid, DCC, DMAP, CH_2Cl_2, Δ, 12 h, 66%, (f) $Me_2C(OMe)_2$, PTSA then CAN, 54%; (g) TPAP/NMO, 91%; (h) EtMgBr, THF, −78 °C, 74%; (i) TPAP, NMO, 73%; (j) THF, −78 °C, CH_2=CHMgBr, 95%; (k) Dowex 50, MeOH, 61%; (l) $PdCl_2$, $CuCl_2$, CO, NaOAc, AcOH; (m) MeOH, K_2CO_3, 60% (2 steps).

Furanolactone **II** should be delivered by subjecting an ene-triol, incorporating both an allylic and nonallylic *tert*-alcohols, to the Pd(II)-mediated cascade. Asymmetry was to be installed using dihydroxylation, as developed by Sharpless. These procedures are now described.

Inexpensive 3-butyn-1-ol (**26**), after protection as the PMP ether **27**, was treated with bromo-9-BBN to give the 2-bromo-1-alkene **28**, which in the presence of $Fe(acac)_3$[21] and ethyl magnesium bromide yielded the protected homoallylic alcohol **29**, ready for asymmetric dihydroxylation. Reaction with AD-mix β provided protected triol **30** of >95% ee, by examination of its Mosher ester **31**, and predicted to be *R*-configured by the Sharpless mnemonic (Scheme 4).[22] This was confirmed by its levo rotation, as the 2-methyl (lower) homologue, of known absolute configuration, is also levo-rotatory.[23] Protected triol **30** was then processed to afford sensitive triol **35**

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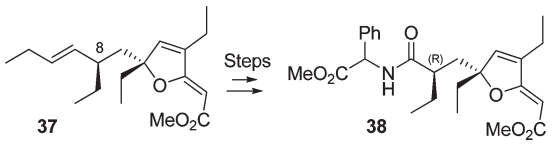
SCHEME 5. Degradative Study of Methyl Ester 37 from *P. halichondroides*



as a mixture of diastereomers, which were subjected to the Pd(II)-lactone forming cascade. Two readily separated furanolactones **36** were formed in good yield (overall 78%) in the ratio 63:37, and NOESY spectra[7] with the benzyl derivatives confirmed that the major lactone possessed the desired *trans*-configuration with the absolute stereochemistry portrayed in Scheme 4. With this lactone available, attention then turned to construction of the side chain, and its linkage to this core.

The C8−C14 Side Chain[24] and Considerations of C10 Chirality. With respect to the likely configuration at C10 in plakortone D (**4**), there was information based on degradative studies with natural methyl ester **37** and synthetic derivative **38** that ethyl bearing C8 was likely to be *R*-configured[25] (Scheme 5).

On the basis that C8 in these compounds has a likely biosynthetic nexus with C10 in plakortone D (**4**), the 10*R* configuration would be likewise favored, although we conveniently acquired both C10 enantiomers of **I** (see Scheme 3) for linkage to the lactone core.

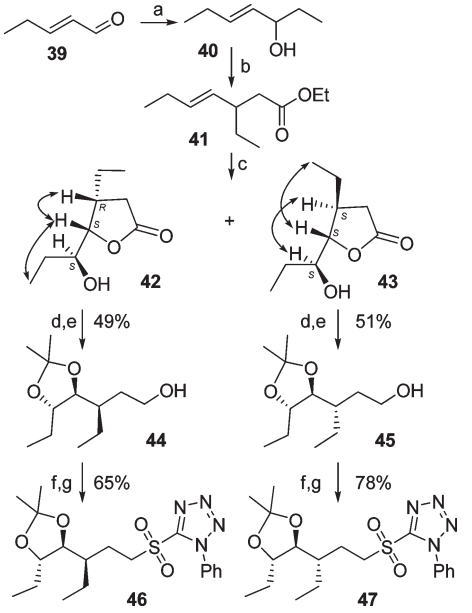
The γ,δ-unsaturated ester **41** (obtained from enol **40** by the Johnson variant of the enolate Claisen rearrangement) on treatment with AD-mix α provided a separable mixture of two lactones, **42** and **43**. NOESY spectra and the X-ray crystal structure of the *p*-nitrobenzoate of **42**, when considered with the mnemonic for predicting the sense of induction in these reactions, led to the absolute stereochemistry shown in Scheme 6.

In confirmation of these conclusions, (*S*,*S*)-hydroxylactones of this type are dextrorotatory and **42** and **43** have $[\alpha]_D$ of +38.6 and +20.3, respectively.[26] The separated lactones were then reduced ($LiAlH_4$) to the 1,4,5-triols, with the 4,5-diol subunit then protected as the acetonide, to afford **44** and **45**, epimeric at the center destined to become C10 in plakortone D (**4**). The modified sulfones **46** and **47**, generated from the sulfides (with 1-phenyl-1*H*-tetrazole-5-thiol) by oxidation with peroxide and molybdate,[27] were selected as carbanionic precursors for coupling with the furanolactone aldehyde (3*S*,4*S*,6*R*)-**48**.

Lactone−Side Chain Coupling. The hydroxymethyl *trans*-lactone (3*S*,4*S*,6*R*)-**36** was oxidized (Swern) to the aldehyde **48**, which was immediately coupled with the anion of sulfone **46**, generated with KHMDS in THF. After workup, flash chromatography afforded pure lactone **49**. Acetonide removal liberated the (C7−C8)-unsaturated 11,12-diol and mild hydrogenation furnished key diol **50** with $[\alpha]_D$ −26.3. Sulfone **47**, the epimer of **46**, was likewise coupled with the same aldehyde (3*S*,4*S*,6*R*)-**48**, to provide diol **51**, with $[\alpha]_D$ −25.5 (Scheme 7).

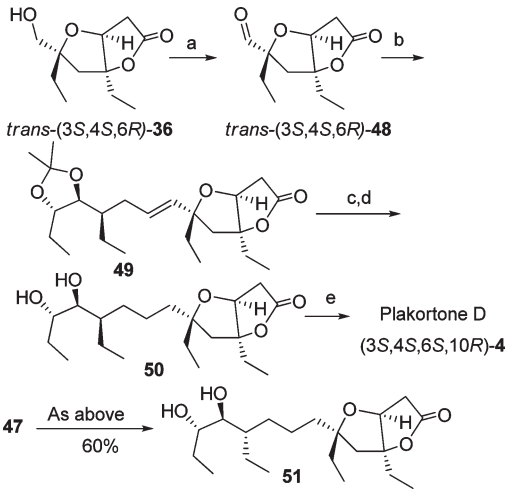
Diols of this constitution, presciently from our point of view, were prepared by Patil and co-workers[2] from their natural plakortone D (**4**) with both AD-mix α and AD-mix β, in the hope that increased polarity in the side-chain would enhance activity and hydrophilicity. Regrettably, the diols, unlike plakortone D (**4**) itself, showed no effect on SR-Ca^{2+} uptake. However, these conversions of natural plakortone D

SCHEME 6. Synthesis of Sulfones 46 and 47[a]



[a]Reagents and conditions: (a) EtMgBr, Et_2O, 0 °C, 88%; (b) $CH_3C(OEt)_3$, H^+, Δ, 68%; (c) AD-mix α, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 0 °C, 48 h, 90%; (d) $LiAlH_4$, Et_2O; (e) $Me_2C(OMe)_2$, PTSA; (f) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3; (g) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2.

SCHEME 7. Synthesis of Diols 50 and 51 and Plakortone D (4)[a]



[a]Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −40 °C, 60%; (b) KHMDS/THF, −78 °C, **46**, 54%; (c) MeOH, PTSA, 82%; (d) H_2, PdC, hexane, 83%; (e) $HC(OEt)_3$, Δ, 60%.

(24) The racemic C8−C14 side chain was constructed from ester **41**, converted to its phosphorane, and coupled with the aldehyde acquired from *trans*-(3*S*,4*S*,6*R*)-**36** to yield 7,8-dehydroplakortone D. Attempts at regioselective reduction of the 7,8-double bond were not successful. This information is presented in the Supporting Information.

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TABLE 1. NMR Data ($CDCl_3$) for Synthesized 50 and 51 and Diol Derived from Natural Plakortone D (4)

	(*S*,*S*) diol derived from natural **4**[2]		**50** ($[\alpha]_D$ −26.3)		**51** ($[\alpha]_D$ −25.5)	
position	δ_H [*J* in Hz]	δ_C	δ_H [*J* in Hz]	δ_C	δ_H [*J* in Hz]	δ_C
1		175.6		175.4		175.5
2	2.71, dd, 4.5, 18.3	37.4	2.69, dd, 4.7, 18.3	37.4	2.69, dd, 4.6, 18.3	37.5
	2.64, dd, 1.0, 18.3		2.63, brd, 18.3		2.63, dd, 0.8, 18.3	
3	4.34, dd, 1.1, 4.5	80.6	4.33, dd, 0.7, 4.6	80.6	4.33, dd, 1.1, 4.5	80.6
4		97.8		97.7		97.7
5	2.29, d, 14.4	45.2	2.28, d, 14.4	45.2	2.27, d, 14.4	45.1
	1.89, d, 14.4		1.87, d, 14.4		1.87, d, 14.4	
6		87.4		87.4		87.4
7	1.48, m	38.9	1.47, m	38.8	1.51, m	38.9
					1.41, m	
8	1.42, m[a]	21.4	1.28, m	21.4	1.40, m	23.0
	1.28, m[a]					
9	1.42, m[a]	30.2	1.35, m	30.2	1.43, m	28.9
	1.28, m[a]				1.28, m	
10	1.40, m	41.3	1.41, m	41.2	1.39, m	41.4
11	3.37, dd, 4.2, 5.2	75.3	3.37, dd, 4.2, 4.6	75.3	3.37, t, 4.5	75.0
12	3.54, dt, 4.2, 6.8	73.4	3.54, dt, 4.6, 8.1	73.4	3.53, dt, 4.9, 8.1	73.3
13	1.56, m	26.8	1.55, m	26.8	1.55, m	26.8
	1.42, m		1.42, m		1.44, m	
14	0.98, t, 7.4	9.9	0.97, t, 7.4	9.9	0.97, t, 7.4	9.9
15	1.56, m	31.3	1.57, m	31.2	1.57, m	31.3
16	0.85, t, 7.4	8.5	0.83, t, 7.4	8.5	0.83, t, 7.4	8.5
17	1.74, m	30.4	1.74, m	30.4	1.73, m	30.4
18	1.01, t, 7.4	8.6	1.02, t, 7.4	8.6	1.00, t, 7.4	8.6
19	1.42, m	21.1	1.47, m	21.1	1.27, m	21.6
			1.32, m			
20	0.90, t, 7.4	11.6	0.89, t, 7.4	11.6	0.88, t, 7.4	11.3

[a]Incorrectly assigned chemical shifts.

(**4**) to diols, with $[\alpha]_D$ −27.3 from AD-mix α and $[\alpha]_D$ −9.8 from AD-mix *β*, and assigned as the α (*R*,*R*) and *β* (*S*,*S*) stereoisomers, respectively,[2] assist stereochemical assignments in our synthetic systems. However, correct application of the Sharpless mnemonic[22] requires Patil's assignments to be reversed, so that the AD-mix α-derived diol with $[\alpha]_D$ −27.3 is (*S*,*S*). Our diol **50**, necessarily constrained to be (*S*,*S*) configured by the manner of its construction, exhibited $[\alpha]_D$ −26.3, in good agreement. As shown in Table 1, the ^{13}C NMR data for our synthesized diol **50** matched with high precision that for the (*S*,*S*)-diol (using AD-mix α) from natural plakortone D (**4**), but clearly less well for epimeric (at C10) diol **51**, e.g. C8, C9, C19, and C20. Therefore, the C10 ethyl bearing center in plakortone D (**4**) is *R*-configured, as considered likely[25] from the data for the natural methyl ester **37**.

Manipulation of diol **50** by stereospecific *syn* removal of the 1,2-diol unit and creation thereby of the *E*-double bond would yield plakortone D (**4**). An attractive procedure for such a manouevre was reported by Crank and Eastwood in their early pyrolytic studies.[28] In the prescribed manner,[28] diol **50** was reacted with triethyl orthoformate at 150 °C for 3 h, with removal of ethanol, and the resulting crude ortho compound was heated at 180 °C for 1 h. (Elimination to provide the desired alkene occurred under GC-MS conditions.) The pure alkene (60%) was obtained after flash chromatography and the ^1H and ^{13}C NMR (see Table 2) and mass spectra matched those for authentic plakortone D (**4**).[29,30] The specific rotation, $[\alpha]_D$ −24.5, for synthetic material was also in good agreement with that of isolated **4** ($[\alpha]_D$ −26.3).[2] Consequently, plakortone D (**4**) has the structure and absolute stereochemistry portrayed in Figure 2 and its acquisition demonstrated (1) the likely utility of the Pd(II)-induced cascade in the synthesis of other plakortones and (2) stereochemical

TABLE 2. NMR Data ($CDCl_3$) for Synthesized and Natural Plakortone D (4)

	natural plakortone D (**4**)[2]		synthetic plakortone D (**4**)	
position	δ_H [*J* in Hz]	δ_C	δ_H [*J* in Hz]	δ_C
1		175.5		175.6
2	2.70, dd, 4.4, 18.3	37.4	2.68, dd, 4.4, 18.3	37.4
	2.63, dd, 1.3, 18.3		2.62, dd, 1.3, 18.3	
3	4.33, dd, 1.3, 4.4	80.5	4.32, dd, 1.3, 4.4	80.6
4		97.8		97.8
5	2.26, d, 14.4	45.0	2.24, d, 14.4	45.0
	1.89, d, 14.4		1.87, d, 14.4	
6		87.5		87.5
7	1.53, m	38.4	1.51, m	38.4
	1.35, m		1.35, m	
8	1.21, m	21.5	1.17−1.24, m	21.5
	1.16, m			
9	1.32, m	35.4	1.30, m	35.4
	1.18, m		1.17, m	
10	1.76, m	44.3	1.76, m	44.3
11	5.07, ddt,1.5, 8.9,15.3	133.2	5.05, ddt, 1.5, 8.9, 15.3	133.2
12	5.38, dt, 6.4, 15.3	132.3	5.39, dt, 6.3, 15.3	132.3
13	2.00, m	25.6	1.99, m	25.7
14	0.97, t, 7.4	14.2	0.95, t, 7.4	14.3
15	1.55, m	31.4	1.55, m	31.5
16	0.84, t, 7.4	8.4	0.83, t, 7.4	8.4
17	1.74, m	30.3	1.73, m	30.4
18	1.02, t, 7.4	8.6	1.00, t, 7.4	8.6
19	1.35, m	28.3	1.34, m	28.3
	1.18, m		1.17, m	
20	0.82, t, 7.4	11.7	0.80, t, 7.4	11.7

(28) Crank, G.; Eastwood, F. W. *Aust. J. Chem.* **1964**, *17*, 1392.

(29) Copies of spectra of plakortone D and the derived C11,12 diols were kindly provided by Drs. Patil and Freyer of Glaxo-Smith-Kline.

(30) Pr. J. Boukouvalas (Laval University) has presented a synthesis of plakortone D (see abstract OE9, 38th IUPAC Congress Frontiers in Chemistry, Word Chemistry Congress 2001, Brisbane).

TABLE 3. ^{1}H NMR Spectral Data ($CDCl_3$) of Natural Plakortone E (**5**) and Synthetic Diastereomers **53**−**56**

	5[3]	**53** or **55** (**I**)	**53** or **55** (**II**)	**54** or **56** (**III**)	**54** or **56** (**IV**)
2	2.70, dd, 18.0, 4.8	2.67, dd, 18.0, 4.8	2.66, dd, 18.2, 5.0	2.67, dd, 18.2, 4.6	2.67, dd, 18.3, 4.7
	2.63, bd, 18.0	2.60, bd, 18.0	2.61, bd, 18.2	2.62, dd, 18.2, 1.0	2.61, bd, 18.3, 0.5
3	4.31, bd, 4.8	4.33, dd, 4.7, 0.6	4.30, dd, 5.0,0.8	4.27, dd, 4.6,1.2	4.23, dd, 4.7, 0.95
5	2.18, d, 14.6	2.21, d, 14.5	2.15, d, 14.5	2.37, d, 14.3	2.27, d, 14.5
	1.97, d, 14.6	2.04, d, 14.5	1.95, d, 14.5	1.85, d, 14.3	1.79, d, 14.5
7	1.62, m	1.58, m	1.59, m	1.61, dd, 14.3, 7.9	1.55, dd, 14.3, 7.2
	1.45, dd, 13.2, 9.0	1.57, dd, 14.3, 9.0	1.43, dd, 14.2, 9.2	1.48, m	1.62, m
8	1.92, m	1.91, m	1.89, m	1.86, m	1.85, m
9	5.09, dd, 15.3, 9.0	5.13, ddt, 15.3, 9.0, 1.4	5.07, ddt, 15.3, 9.3, 1.5	5.10, ddt, 15.3, 9.0, 1.5	5.07, ddt, 15.3, 9.3, 1.4
10	5.38, dt, 15.3, 6.2	5.35, dt, 15.3, 6.3	5.38, dt, 15.3, 7.0	5.35, dt, 15.3, 6.3	5.33, dt, 15.3, 6.3
11	2.00, m	1.98, dqd, 7.5, 7.5, 1.5	2.00, dqd, 7.3, 7.3, 1.0	1.98, dqd, 7.5, 7.5, 1.4	2.00, m
12	0.97, t, 7.6	0.94, t, 7.4	0.94, t, 7.5	0.94, t, 7.5	0.94, t, 7.5
13	1.63, m	1.59, m	1.50−1.64, m	1.46−1.54, m	1.41−1.55, m
	1.57, m	1.54, m			
14	0.85, t, 7.6	0.82, t, 7.4	0.82, t, 7.5	0.82, t, 7.5	0.83, t, 7.4
15	1.76, dq, 15.3, 6.9	1.73, dq, 14.2, 7.4	1.65−1.77, m	1.74, dq, 14.3, 7.2	1.63−1.76, m
	1.70, dq, 15.3, 6.9	1.67, dq, 14.2,7.4		1.70, dq, 14.3, 7.4	
16	1.00, t, 6.9	0.98, t, 7.4	0.98, t, 7.5	0.99, t, 7.5	0.97, t, 7.4
17	1.40, dq, 13.9, 6.9	1.35, m	1.38, m	1.36, m	1.34, m
	1.21, dq, 13.9, 6.9	1.24, m	1.21, m	1.17, m	1.19, m
18	0.82, t, 6.9	0.80, t, 7.4	0.80, t, 7.5	0.78, t, 7.5	0.79, t, 7.4

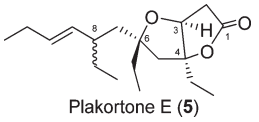


FIGURE 4. Structure of plakortone E (**5**).

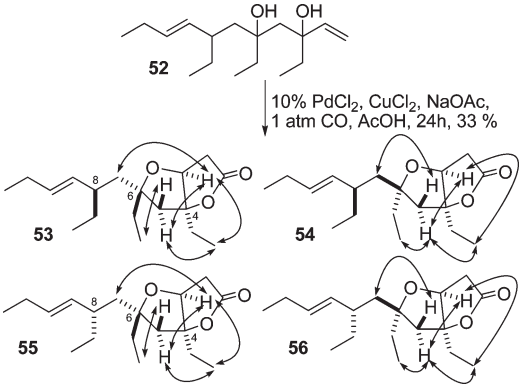


FIGURE 5. Selective NOE correlations for the diastereomers **53**−**56** of plakortone E (**5**).

guidance for them, assuming a similar biosynthetic pedigree. We were therefore encouraged to extend synthetic work to other members of the family.

Plakortone E. Plakortone E (**5**) (Figure 4) is a lower bis-homologue of plakortone D (**4**) and among the series B−F (**2**−**6**), which are all cytotoxic,[3] this plakortone is the most active. The relative stereochemistry about the bicyclic core was based on a 2D ROESY spectrum, but was not related to the C8 configuration. The determination for plakortone D (**4**), however, would suggest C8 to be *R*-configured.

The sequence employed for acquisition of the four racemic diastereomers of plakortone E (**5**)[8] again utilizes the Pd(II)-based cascade but unlike the approach to plakortone D (**4**), the complete acyclic carbon skeleton was assembled first and then subjected to the Pd(II) conditions. This was partly because we believed stereodefined acyclic precursors of this type could be acquired and thence deliver enantiomers of plakortone E (**5**).

TABLE 4. ^{13}C NMR spectral data ($CDCl_3$) of Natural Plakortone E (**5**) and Synthetic Diastereomers **53**−**56**

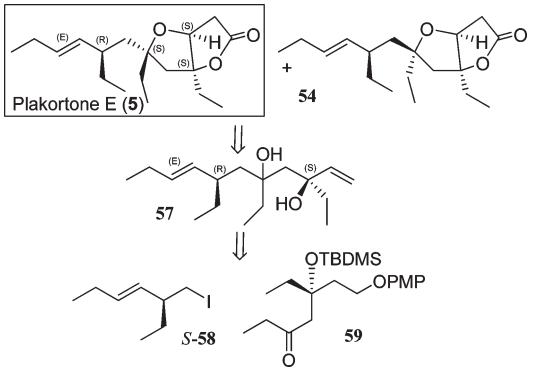
	5[3]	**53** or **55** (**I**)	**53** or **55** (**II**)	**54** or **56** (**III**)	**54** or **56** (**IV**)
1	175.5	175.6	175.6	175.5	175.6
2	37.5	37.6	37.5	37.3	37.4
3	80.2	80.8	80.0	79.9	79.5
4	98.0	97.9	97.9	97.9	98.1
5	46.2	44.6	46.0	45.4	47.2
6	88.2	87.7	87.7	87.5	87.3
7	43.6	43.4	43.5	43.0	43.7
8	40.7	40.5	40.8	40.6	41.1
9	133.1	134.3	133.8	134.2	134.0
10	132.0	131.7	131.8	131.6	131.8
11	25.5	25.5	25.5	25.5	25.5
12	13.9	13.9	13.9	13.9	13.9
13	31.7	32.8	31.7	31.4	30.5
14	8.4	8.5	8.3	8.1	7.9
15	30.5	30.2	30.4	30.5	30.4
16	8.5	8.6	8.6	8.5	8.5
17	29.6	30.0	29.7	29.9	29.7
18	11.7	11.6	11.6	11.6	11.6

The required diene-diol **52** was acquired as a stereoisomeric mixture,[8] and the key cyclization−carbonylation steps proceeded satisfactorily with this sensitive enediol to afford HPLC-separable diastereomers **53**−**56** (Figure 5), all as racemates. Detailed NMR studies (NOESY spectra) permitted the four isomers to be grouped[8] into two sets of two, on the basis of the *trans* or *cis* relationship of ethyl groups at C4 and C6. These subsets, with defining NOE's, are shown below, with the relative stereochemistry at C8 again not established.

A full listing of the ^{1}H and ^{13}C NMR spectral data is shown in Tables 3 and 4. Careful comparisons of these data confirm that the second eluting isomer (**II**) under our HPLC conditions is spectroscopically identical with the natural compound, which therefore is one of the two *trans*-systems, **53** or **55**. The most noticeable difference in NMR shifts between **53** and **55** concerned C5 and H7 (Table 3 and 4). The reported[3] shift for C8 (45 ppm) in natural plakortone E (**5**) has been corrected to δ 40.7, on the basis of the HSQC spectrum kindly provided by Professor Fattorusso.

The demonstrated configuration of plakortone D (**4**) indicates that an enantioselective synthesis of plakortone E (**5**) would result from the transformation in Scheme 8, which

SCHEME 8. Retrosynthetic Analysis of Plakortone E (5)



would deliver two separable stereoisomers, configurationally defined at the C8 position, and with NMR assessable ring stereochemistry. One by our reckoning would be natural plakortone E (**5**).

For reasons of convenience, we sought to acquire an epimer of **57** by utilizing the available *R*-**58** rather than *S*-**58** shown in Scheme 8. The protected ketodiol **59** was acquired from **30** (see Scheme 4) as shown in Scheme 9, with asymmetry introduced by asymmetric dihydroxylation of a *p*-methoxyphenyl ether.

Primary iodide *R*-**58** was accessed with configuration control at the ethyl-bearing center, by a sequence originating with (*E*)-hept-4-en-3-ol (**40**). Asymmetric epoxidation based kinetic resolution of the racemic enol furnished *S*-**64**, which was then chain extended with the Johnson−Claisen rearrangement to carboxylic acid **66** (notice there is 1,3-chirality transfer in the **64** to **65** conversion, and a descriptor change at the ethyl-bearing center accompanying coupling of fragments **58** and **59**). The derived Barton ester **67** (from sodium *N*-hydroxythiopyridone) on photolysis in the presence of iodoform provided the required iodide *R*-**58**. Iodide−lithium exchange with *tert*-butyllithium in ether−pentane provided primary lithium species **68**, which on addition to protected ketodiol **59**, afforded the protected, oily triol **69** as a 1:1.4 mixture of diastereomers, in reasonable yield (59%). Deprotection released the triol **70**, which was converted to mesylate **71** and then to the primary bromide **72**.

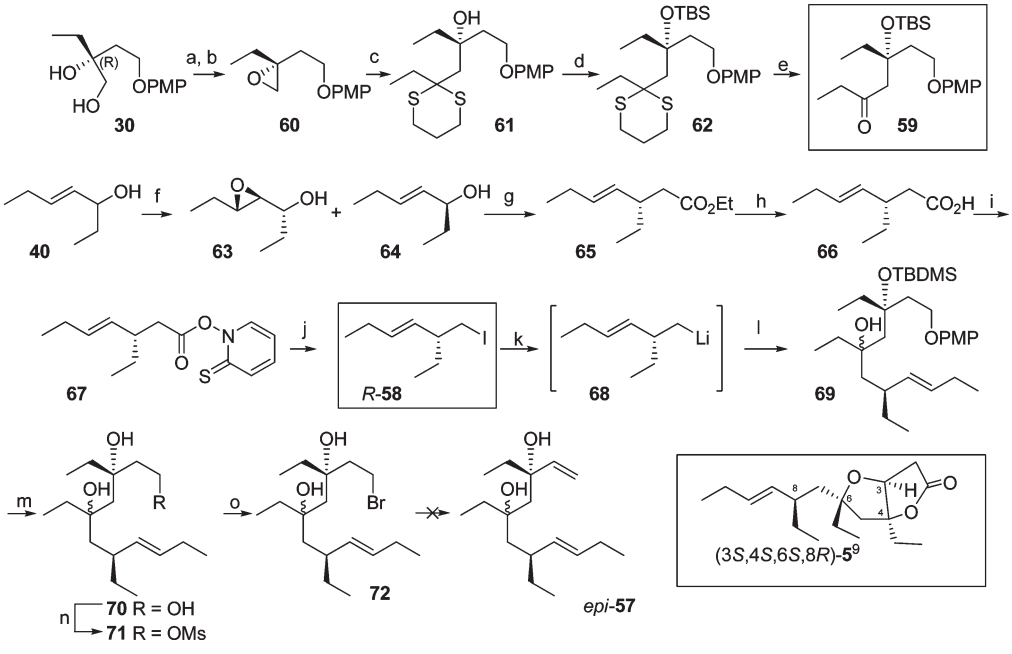
β-Elimination from either **71** or **72** would provide *epi*-**57**, a system already demonstrated[8] in the racemic series to respond well to the Pd(II)-promoted cascade to afford the plakortone E (**5**) system.

Although we were not unmindful that the *tert*-center, γ to the bromo or mesyloxy leaving group, would be retardative to basic β-elimination, it was surprising that not one of a variety of procedures for basic elimination (also via the selenoxide) provided any significant alkene formation. Starting material was generally recovered. Interestingly, an analogous elimination proceeded (with *t*-BuOK in refluxing *t*-BuOH) in a β,γ,γ-trisubstituted primary iodide to yield the terpenoid (+)-amiteol.[31]

An altered approach with earlier introduction of the terminal double bond was required but coincidentally Ohira reported[9] a conceptually very different synthesis of plakortone E (**5**) and after comparison with our spectral data of **53** and **55**, settled its absolute stereochemistry as (3*S*,4*S*,6*S*,8*R*) (shown in Scheme 9) as suggested by us.[8] With the absolute configuration of **5** settled, we turned to the more complex congeners, plakortones C (**3**) and F (**6**).

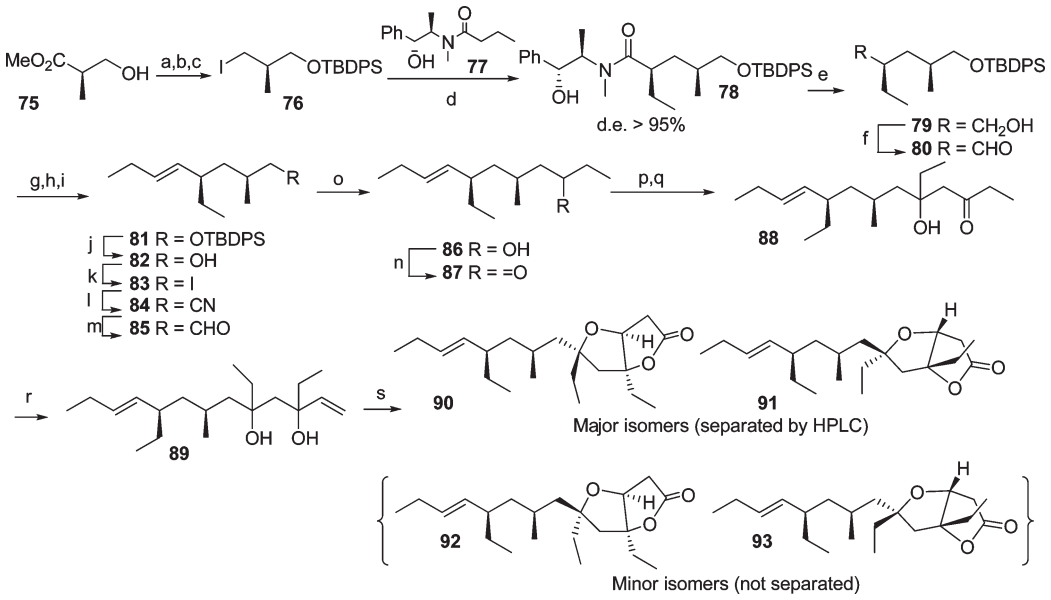
Plakortone C. Plakortone C (**3**) resembles plakortone D (**4**) but incorporates methyl substitution at C8, presumably

SCHEME 9. Synthesis of Bromide 72[a]



[a]Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2; (b) K_2CO_3, MeOH, H_2O (91% over 2 steps); (c) 2-ethyl-1,3-dithiane, ^{n}BuLi, Et_2O, 0 °C, 5 h, 92%; (d) TBDMSOTf, Et_3N, CH_2Cl_2; (e) Storke's reagent [$(CF_3CO_2)_2IPh$], $CaCO_3$, MeOH:H_2O 9:1, 86% over 2 steps; (f) (−)-DIPT, TBHP, $Ti(iOPr)_4$, CH_2Cl_2, 61%; (g) $CH_3C(OEt)_3$, propionic acid, Δ; (h) NaOH, MeOH, H_2O, 59% over 2 steps; (i) $(COCl)_2$, CH_2Cl_2, sodium 2-thioxopyridin-1(2*H*)-olate, 98%; (j) CHI_3, *hv*, CCl_4, 86%; (k) ^{n}BuLi, −78 °C, pentane:Et_2O 3:2; (l) Et_2O, **59**, 59%; (m) CAN, MeOH, 71%; (n) MsCl, Et_3N, 0 °C, CH_2Cl_2; (o) LiBr, THF, Δ, 64% over 2 steps.

SCHEME 10. Synthesis of Plakortone C (90) and *epi*-Plakortone C (91)[a]



[a]Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 0 °C to rt, 5 h; (b) DIBAL, toluene, −78 °C to rt, 2 h (89% two steps); (c) PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C to rt, 2 h (88%); (d) LDA, LiCl, THF, 0 °C to rt, 24 h (85%); (e) LiH_2NBH_3, THF, 0 °C to rt, 8 h (97%, de >95%); (f) $(COCl)_2$, CH_2Cl_2, DMSO, −78 °C; Et_3N, −78 °C to rt (75%); (g) $C_2H_5CH_2SO_2Ph$, *n*-BuLi, THF, −78 °C; (h) Ac_2O, Et_3N, DMAP; (i) Mg, $HgCl_2$, EtOH, rt, 42% three steps, *E*:*Z* 11:1; (j) TBAF, THF, rt, 92%; (k) I_2, PPh_3, imidazole, toluene, rt, 100%; (l) NaCN, DMF, rt, 79%; (m) DIBAL, Et_2O, −78 to 0 °C, (n) EtMgBr, THF, −78 °C, 73%; (o) $(COCl)_2$, CH_2Cl_2, DMSO, Et_3N, −40 °C, 70%; (p) LDA, THF, −78 °C, CH_3 $C(NNMe_2)CH_2CH_3$; (q) $CuCl_2$, THF−H_2O, 41% over 2 steps; (r) Et_2O, −78 °C, $CeCl_3$, CH_2=$CHMgBr$, 90%; (s) 10% $PdCl_2$, $CuCl_2$, NaOAc, 1 atm CO, AcOH, rt, 24 h, 33%.

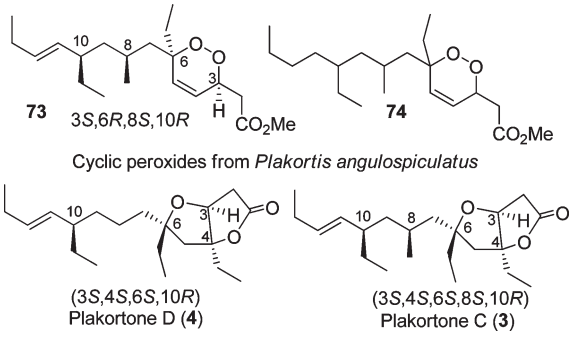


FIGURE 6. Structures of plakortones C (**3**), D (**4**), and related cyclic peroxides **73** and **74**.

reflecting propionate incorporation, rather than acetate, during its biosynthesis. In planning our approach, we examined the report of Yao and Steliou,[32] which described synthetic studies of a cyclic peroxide **73** (Figure 6) isolated from the Caribbean sponge *Plakortis angulospiculatus* (Family Plakinidae), and co-occurring with an 11,12-dihydro relative **74**.[33] These authors, on the basis of partial asymmetric synthesis, diastereomer separation following *syn*-enforced singlet oxygen addition to the appropriately functionalized diene, and NMR comparisons with the natural compound, concluded that the natural peroxide possessed (3*S*,6*R*,8*S*,10*R*) stereochemistry, as shown in Figure 6. (This stereochemistry would reasonably apply to dihydro-relative **74** as well.) With this intelligence, and assumed biosynthetic similarities,[1] we considered the likely stereochemistry in the side chain of plakortone C (**3**) to be (8*S*,10*R*). The synthetic strategy was to generate this chirality as part of a diene-diol that on experiencing the Pd(II)-induced cascade, would deliver isomers of plakortone C (**3**) of determinable stereochemistry for comparison with the natural compound.

The key elements of the synthesis are summarized in Scheme 10. (*R*)-(+)-3-Hydroxy-2-methylpropionate (**75**) was protected, reduced, and then converted to primary iodide **76**, which alkylated the lithium enolate of the butyramide **77** generated from (1*S*,2*S*)-(+)-pseudoephedrine, to afford the dialkyl-substituted amide **78**. Reduction liberated the (2*R*,4*S*) primary alcohol **79**, the aldehyde **80** from which, with the anion of phenyl propyl sulfone, followed by alcohol deprotection, provided primary alcohol **82**. Derived iodide, (5*R*,7*S*,*E*)-**83**, was chain extended to the nitrile **84**, the aldehyde **85** from which, on reaction with ethylmagnesium bromide yielded the secondary alcohol **86** as a 60/40 diastereomeric mixture. Swern oxidation provided ketone **87**, which with the (kinetic) lithium anion of 2-butanone *N*,*N*-dimethylhydrazone provided a moderate yield of the ketone (7*S*,9*R*,*E*)-**88**. This ketone, with $CeCl_3$−vinylmagnesium bromide afforded, in apparently good yield, ostensibly the diene-diol **89**, which was immediately subjected to the Pd(II)-promoted sequence with CO. The resulting furanolactones, **90**−**93** (GC-MS) on flash chromatography, provided two fractions: a mixture (50 mg) of the major isomers **90** and **91** and a mixture (15 mg) of the four possible isomers, **90**−**93**. Part of the former mixture was subjected to HPLC separation and provided pure samples of the two major lactones. These two lactones were characterized by NMR methods and both had a *trans*-arrangement of ethyl groups about the *cis*-fused bicyclic

(31) Kesselmans, R. P. W.; Wijnberg, J. B. P. A.; Minnaard, A. J.; Walinga, R. E.; De Groot, A. *J. Org. Chem.* **1991**, *56*, 7237.
(32) Yao, G.; Steliou, K. *Org. Lett.* **2002**, *4*, 485.
(33) Gunasekera, S. P.; Gunasekera, M.; Gunawardana, G. P.; McCarthy, P.; Burres, N. *J. Nat. Prod.* **1990**, *53*, 669.

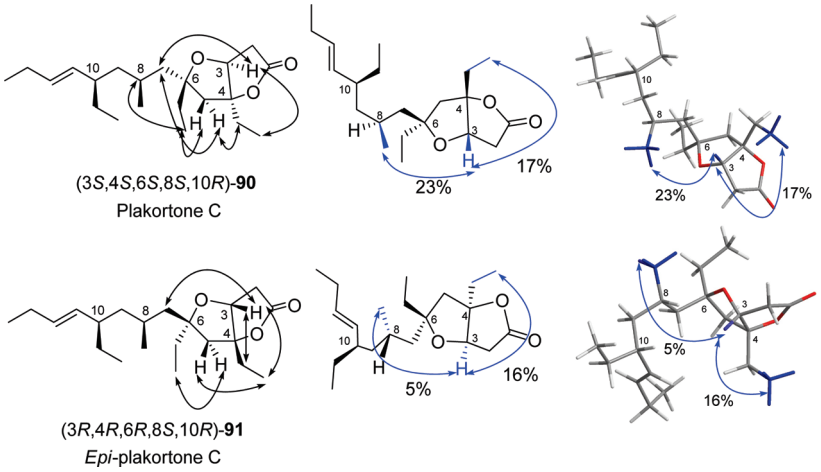


FIGURE 7. Selected NOE correlations for synthetic plakortone C (**90**) and *epi*-plakortone C (**91**) and corresponding 3D structures (Chemdraw).

TABLE 5. ^{1}H and ^{13}C NMR Data ($CDCl_3$) of Plakortone C (**3**) and Synthetic Diastereomers 90 and 91

	natural plakortone C (**3**)[2]		synthetic plakortone C (**90**)		*epi*-plakortone C (**91**)	
	δ_H [*J* in Hz]	δ_C	δ_H [*J* in Hz]	δ_C	δ_H [*J* in Hz]	δ_C
1		175.5		175.6		175.6
2	2.69, dd, 18.2, 4.8	37.4	2.67, dd, 18.3, 4.7	37.5	2.68, brd, 18.0	37.6
	2.61, dd, 18.2, 1.0		2.61, brd, 18.2		2.61, brd, 18.0	
3	4.34, dd, 4.8, 1.0	80.2	4.32, brd, 4.7	80.3	4.31, dd, 4.8, 0.7	80.4
4		97.6		97.7		97.8
5	2.28, d, 14.5	45.9	2.28, d, 14.4	46.0	2.27, d, 14.5	45.9
	1.83, d, 14.5		1.83, d, 14.4		1.86, d, 14.5	
6		88.0		88.1		88.1
7	1.38, d, 5.7	45.9	1.36, d, 5.7	46.0	1.45, dd, 15.0, 5.0	46.2
					1.31, dd, 15.0, 6.3	
8	1.57, m	26.3	1.55, m	26.4	1.55, m	26.4
9	1.20, m	44.7	1.16, m	44.7	1.30, m	44.0
	1.10, m		1.09, m		1.06, m	
10	1.85, m	42.1	1.82, m	42.1	1.82, m	42.3
11	4.99, ddt, 15.3, 9.0, 1.5	133.2	4.98, ddt, 15.3, 9.1, 1.4	133.2	5.00, ddt, 15.1, 9.0, 1.4	133.2
12	5.39, dt, 15.3, 6.4	132.5	5.38, dt, 15.3, 6.3	132.4	5.38, dt, 15.1, 6.2	132.3
13	1.99, m	25.6	1.99, m	25.6	1.98, m	25.6
14	0.95, t, 7.4	14.1	0.95, t, 7.5	14.2	0.94, t, 7.5	14.2
15	1.60, m	31.6	1.58, m	31.6	1.56, m	32.0
16	0.82, t, 7.4	8.6	0.81, t, 7.4	8.7	0.82, t, 7.4	8.6
17	1.74, m	30.3	1.72, m	30.4	1.71, m	30.3
18	1.00, t, 7.4	8.5	0.99, t, 7.4	8.6	0.99, t, 7.4	8.6
19	1.30, m	28.9	1.28, m	29.0	1.28 m	29.0
	1.17, m		1.16, m		1.16, m	
20	0.81, t, 7.4	11.7	0.80, t, 7.4	11.7	0.80, t, 7.4	11.8
21	0.89, t, 6.5	20.7	0.88, t, 6.5	20.8	0.85, t, 6.3	21.0

system, and were therefore **90** and **91** (see Figure 7 for the important NOE's). The former has $[\alpha]_D$ −29.3 and the latter $[\alpha]_D$ +11.5, which are consistent with our determinations for plakortone D (**4**) allowing identification of **90** and **91**. Plakortone C (**3**) has a reported[2] $[\alpha]_D$ −24.9. A full listing of the NMR assignments for natural plakortone C (**3**) and our synthesized products is located in Table 5. It is seen that the data for synthesized **90** with (3*S*,4*S*,6*S*,8*S*,10*R*)-stereochemistry match those for natural plakortone C (**3**), thereby establishing its absolute stereochemistry. *epi*-Plakortone C (**91**) differs from **90** in the chemical shift, and appearance of one H7, one H9, and C9. A long-range NOE effect between H3 and the C8 methyl group was much more pronounced in **90** than in **91**, consistent with the calculated preferred geometries for these stereoisomers, as shown in Figure 7.

Plakortone F. Fattorusso and his group[3] isolated plakortone F (**6**) from the Caribbean sponge *Plakortis simplex*. Spectroscopic data supported its formulation as the 11,12-dihydro derivative of plakortone C (**3**) and confirmed the same relative stereochemistry about the lactone core. The reported optical rotations for plakortones C (**3**) and F (**6**) are $[\alpha]_D$ −24.9 and $[\alpha]_D$ −11, respectively, suggesting likely coincidence of absolute stereochemistry (Figure 8).

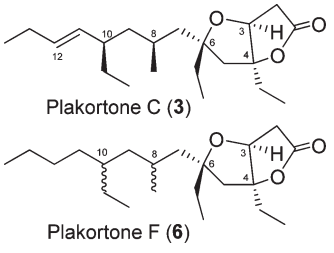


FIGURE 8. Structures of plakortones C (**3**) and F (**6**).

TABLE 6. NMR Spectral Data ($CDCl_3$) of Natural Plakortone F (6) and Synthetic Plakortone F (94) and *epi*-Plakortone F (95)

	natural plakortone F (**6**)[3]		synthetic plakortone F (**94**)		*epi*-plakortone F (**95**)	
position	δ_H [*J* in Hz]	δ_C	δ_H [*J* in Hz]	δ_C	δ_H [*J* in Hz]	δ_C
1		176.0		175.6		175.6
2	2.71, dd, 18.3, 5.1 2.64, dd, 18.3, 0.8	37.2	2.68, dd, 18.3, 4.5 2.62, brd, 18.3	37.3	2.68, dd, 18.3, 5.1 2.62, brd, 18.3	37.5
3	4.35, bd, 5.1	80.5	4.33, dd, 5.1, 0.8	80.1	4.32, dd, 5.1, 0.8	80.3
4		97.9		97.6		97.8
5	2.32, d, 14.7 1.83, d, 14.7	46.2	2.30, d, 14.6 1.82, d, 14.6	46.4	2.29, d, 14.7 1.88, d, 14.7	46.0
6		88.0		88.0		88.0
7	1.41, dd, 14.0, 8.0[a] 1.34, dd, 14.0, 3.7[a]	45.3	1.39, dd, 14.3, 3.2 1.33, dd, 14.3, 7.5	45.4	1.52, dd, 14.1, 4.1 1.27, dd, 14.1, 7.0	46.0
8	1.60, m	31.0[b]	1.56, m	26.4	1.56, m	26.4
9	1.12, m 1.06, m	43.1	1.03−1.08, m	43.4	1.02, m 1.20, m	43.1
10	1.28, m	29.7[c]	1.25, m	36.1	1.22, m	36.3
11	1.24, m	32.3	1.17−1.24, m	32.5	1.20, m	32.5
12	1.26, m	28.5	1.22, m	28.5	1.20, m	28.5
13	1.29, m	22.8	1.29, m	23.2	1.26, m	23.2
14	0.88, t, 7.3	13.4	0.87, t, 7.0	14.2	0.87, t, 7.0	14.2
15	1.29, m 1.22, m	26.6	1.31, m 1.19, m	26.5	1.24, m	26.5
16	0.83, t, 6.6	10.7	0.81, t, 7.2	10.8	0.81, t, 7.2	10.9
17	0.93, d, 6.6	21.8	0.91, d, 6.5	21.5	0.88, d, 6.5	21.9
18	1.62, m 1.58, m	26.8[b]	1.63, m 1.56, m	31.1	1.56, m	31.9
19	0.87, t, 7.3	8.7	0.84, t, 7.6	8.7	0.84, t, 7.6	8.5
20	1.77, m 1.74, m	30.3	1.70, m 1.79, m	30.5	1.71, m	30.4
21	1.02, t, 7.3	8.3	1.00, t, 7.6	8.6	1.00, t, 7.6	8.6

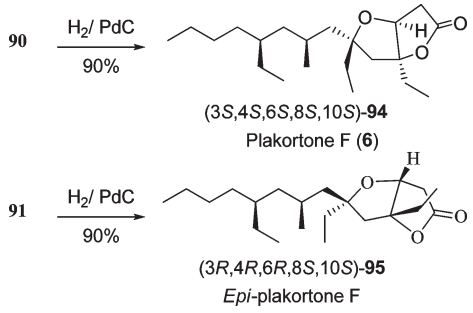
[a]H-7a and H-7b coupling constants have been interchanged in the original paper. [b]The chemical shifts of C8 and C18 have been interchanged in the original paper. [c]Incorrect chemical shift.

Having established the structure and absolute stereochemistry of plakortone C (**3**), the truth of the deduction[2] that plakortone F (**6**) is its 11,12-dihydro relative is open to testing. Mild reduction of pure plakortone C (H_2, Pd−C, hexane, 1 h) provided a **single** dihydro derivative **94** that was spectroscopically identical (^{1}H NMR, see Table 6) with natural plakortone F (**6**), thus confirming its constitution and absolute stereochemistry.[34] Our measured optical rotation, $[\alpha]_D$ −24.0, differs somewhat from that reported for the natural compound, $[\alpha]_D$ −11, but this could be ascribed to the difficulty of working with the low concentration available from the natural source.[35] (Our synthesized plakortone C (**3**) has $[\alpha]_D$ −29.3, with that reported for the natural compound as $[\alpha]_D$ −24.9.)

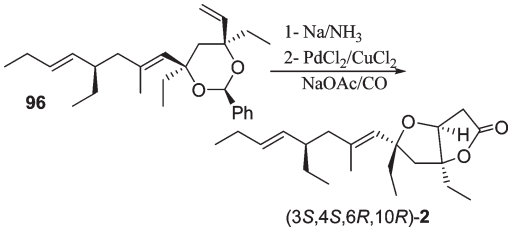
A sample of *epi*-plakortone C **91** ($[\alpha]_D$ +11.5) (with alternate disposition of the *trans* ethyl groups compared with plakortone C (**3**)) was similarly hydrogenated to provide *epi*-plakortone F, **95** ($[\alpha]_D$ +3.4). These conversions are shown in Scheme 11.

Conclusions and Future Prospects. Our exploration of the plakortone E (**5**) synthesis had been driven by the hypothesis that acquisition of an essentially complete, stereochemically pure, carbon framework of a plakortone which incorporated the enediol for Pd(II)-induced furanolactone formation would allow direct access to these interesting natural products. This hypothesis was validated in 2006 by Semmelhack's[10] synthesis of plakortone B (**2**) in which a trienediol that represented the complete carbon framework of **2** was acquired and subsequently underwent Pd(II)-mediated formation of the bicyclic furanolactone core and spectroscopic comparisons with natural plakortone B (**2**) and stereochemical

SCHEME 11. Synthesis of Plakortone F (94) and *epi*-Plakortone F (95)



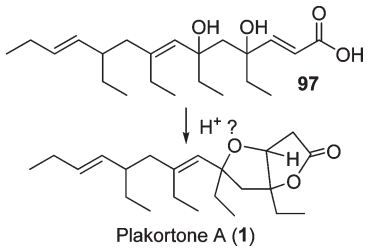
SCHEME 12. Final Step in Semmelhack's Synthesis[10] of Plakortone B (2)



(34) This assumes there was no stereochemical compromise, e.g., at the allylic ethyl bearing position during the mild hydrogenation, consistent with the formation of a single dihydro derivative.

(35) Communication from Professor Fattorusso, January 2010: The small discrepancies in the absolute values can be explained by the fact that we have registered our optical rotation on a very small amount (about 1 mg) of a not absolutely pure substance.

SCHEME 13. Possible Natural Precursor of Plakortone A (1)



precedent,[7] defined the stereochemistry of plakortone B (**2**) as shown in Scheme 12.[36]

Finally, it is germane to consider whether the isolated plakortones may be artifacts resulting from acid-induced furanolactonization of suitable unsaturated dihydroxy acids. This notion is encouraged by the work of Rudi and Kashman,[37] who characterized C8 alkylated (methyl, ethyl) acids such as 4,6-dihydroxy-4,6,8,10-tetraethyltetradec-2,7,11-trienoic acid **97**, but no plakortones from *P. halichondrioides*. As shown in Scheme 13, acid-promoted furanolactonization is feasible, and this particular acid could yield plakortone A (**1**), with no stereochemistry implied.

Syntheses of plakortones D, C, F, and (racemic) E are described and with other information for plakortones B and E establish the constitutions and absolute stereochemistries of these five sponge-derived biologically active secondary metabolites. A palladium(II) triggered furanolactonization, in the presence of carbon monoxide, has been exploited to deliver the fused, bicyclic, sterically congested emblematic "core" or "structural motif" of the series. The possibility that some or all of the known plakortones are artifacts, resulting from acid-induced furanolactonization of natural alkyl-substituted, dihydroxy, unsaturated fatty acids is briefly considered.

Experimental Section

General Methods. Optical rotations were measured at 25 °C, using a 1 mL cell with a 10 cm path length. NMR spectra were recorded on 500 or 400 MHz spectrometers. ^{1}H and ^{13}C signals were recorded in parts per million (ppm) on the δ scale, with the residual solvent peaks ($CDCl_3$: δ_H 7.24 and δ_C 77.0; C_6D_6: δ_H 7.15 and δ_C 128.0) as internal references. HRESIMS were recorded on a MicrOTof-Q spectrometer (ESI mode). ESIMS were recorded on an ion trap spectrometer (ESI mode). HPLC purification was carried out on a HPLC system equipped with a RI detector and a Luna Silica (2) column (250 × 4.6 mm, 100) with 5% ethyl acetate in hexane as an eluent, at a flow rate of 2 mL/min. Flash chromatography separations were performed with silica gel (Silica gel 60, 0.04−0.06 mm, 230−400 mesh ASTM). Melting points were performed on a melting-point apparatus (Dr. Tottoli) and are uncorrected.

General Procedure: Hydroxycyclization−Carbonylation−Lactonization Sequence. NaOAc (3 equiv) and $CuCl_2$ (3 equiv) were added to a dry three-necked flask containing glacial acetic acid (4.5 mL). The solution was stirred until the solid dissolved, and then the unsaturated diol (0.6 mmol) in acetic acid (1 mL) was added. While the contents were stirred vigorously, the flask was purged several times with nitrogen initially and then carbon monoxide through a balloon. A catalytic amount of $PdCl_2$ (0.1 equiv) was added, and stirring was continued. After refilling the balloon with CO, the reaction was stirred overnight at room temperature. This resulted in a color change from bright green to a dull brown. After discharging the carbon monoxide, water (20 mL) was added and the solution turned black. This solution was neutralized with solid $NaHCO_3$ until effervescence ceased. Extraction of the neutralized solution with EtOAc (3 × 20 mL), followed by removal of the solvent gave the crude bicyclic lactones.

Synthesis of 93−102 from (*R*)-(+)-3-Hydroxy-2-methylpropionate (75). Compounds **76−85** were synthesized following literature procedures for the synthesized stereoisomer.[32]

(2*R*)-3-*tert*-Butyldiphenylsilyloxy-2-methylpropyl Iodide (76). This compound was synthesized in 88% yield. Spectroscopic data of **76** matched those of the previously known (*S*)-enantiomer[5] $[\alpha]^{22}_D$ −3.3 (*c* 0.6, $CHCl_3$) (reported[32] for the (*S*)-enantiomer: $[\alpha]^{23}_D$ +3.18 (*c* 7.0, $CHCl_3$)).

(2*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-ethyl-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,4-dimethylpentanamide (78): Yield 85%. $[\alpha]^{22}_D$ +31.7 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, C_6D_6) δ 0.80 (t, *J* = 7.4 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.87 Hz, 3H), 1.06−1.13 (m, 1H), 1.16−1.21 (s and m, 11H), 1.26−1.36 (m, 1H), 1.55−1.71 (m, 2H), 1.91−1.98 (m, 1H), 2.31 (s, 3H), 2.31−2.33 (m, 1H), 3.46 (dd, *J* = 6.5, 9.8 Hz, 1H), 3.57 (dd, *J* = 5.2, 9.8 Hz, 1H), 4.52 (t, *J* = 6.2 Hz, 1H), 7.05−7.11 (m, 1H), 7.21−7.32 (m, 10H), 7.77−7.81 (m, 1H). ^{13}C NMR (100 MHz, C_6D_6) δ 11.9, 14.5, 17.2, 19.6, 26.8, 27.2, 33.8, 36.5, 41.1, 60.0, 69.5, 76.4, 126.7, 127.3, 128.3, 129.9, 134.30, 134.34, 136.0, 143.9, 177.8. Anal. Calcd for $C_{34}H_{48}NO_3Si$: C 74.82, H 8.68, N 2.57. Found: C 74.55, H 9.03, N 2.43.

(2*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-ethyl-4-methylpentan-1-ol (79): Yield 97%. $[\alpha]^{22}_D$ −9.6 (*c* 0.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J* = 7.4 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 9H), 1.16−1.56 (m, 5H), 1.68−1.73 (m, 1H), 3.40−3.53 (m, 4H), 7.33−7.42 (m, 6H), 7.63−7.66 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 17.4, 19.3, 24.2, 26.9, 33.4, 34.4, 39.4, 65.2, 69.2, 127.6, 134.0, 135.6. HR-MS *m*/*z* calcd $[M+Na]^+$ for $C_{24}H_{37}O_2SiNa$ 407.2382, found 407.2377.

(2*R*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-2-ethyl-4-methylpentanal (80): Yield 75%. $[\alpha]^{22}_D$ −7.71 (*c* 0.97, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 7.4 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 9H), 1.16 (ddd, *J* = 14.2, 9.0, 4.7 Hz, 1H), 1.52−1.69 (m, 3H), 1.88 (ddd, *J* = 14.2, 9.1, 4.9 Hz, 1H), 2.18−2.25 (m, 1H), 3.44 (d, *J* = 5.3 Hz, 2H), 7.33−7.43 (m, 6H), 7.61−7.64 (m, 4H), 9.47 (d, *J* = 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 16.7, 19.3, 22.6, 26.8, 32.4, 33.5, 51.0, 68.8, 127.6, 129.6, 133.8, 135.6, 205.6. HR-MS *m*/*z* calcd $[M+Na]^+$ for $C_{24}H_{35}O_2$-SiNa 405.2226, found 405.2220.

***tert*-Butyl((2*S*,4*R*,*E*)-4-ethyl-2-methyloct-5-enyloxy)diphenylsilane (81):** Yield 42% over 3 steps. $[\alpha]^{22}_D$ +11.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.3 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 7.4 Hz, 3H), 1.02 (s, 9H), 1.11−1.20 (m, 1H), 1.22−1.35 (m, 3H), 1.62−1.71 (m, 1H), 1.80−1.88 (m, 1H), 1.94−2.20 (m, 2H), 3.40 (dd, 9.8, 6.3 Hz, 1H), 3.45 (dd, *J* = 9.8, 6.2 Hz, 1H), 4.99 (ddt, *J* = 15.2, 8.9, 1.5 Hz, 1H), 5.36 (dt, *J* = 15.2, 6.3 Hz, 1H), 7.33−7.41 (m, 6H), 7.63−7.65 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 14.2, 16.3, 19.3, 25.6, 26.9, 29.0, 33.3, 38.8, 41.9, 69.7, 127.5, 129.4, 132.0, 133.4, 134.2, 135.6. HR-MS *m*/*z* calcd $[M+Na]^+$ for $C_{27}H_{40}OSiNa$ 431.2746, found 431.2741.

(2*S*,4*R*,*E*)-4-Ethyl-2-methyloct-5-en-1-ol (82): Yield 92%. $[\alpha]^{22}_D$ −21.1 (*c* 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.5 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 7.3 Hz, 3H), 1.08−1.02 (m, 1H), 1.08−1.41 (m, 4H), 1.60−1.66 (m, 1H), 1.84−1.91 (m, 1H), 1.95−2.01 (m, 2H), 3.38 (dd, *J* = 10.4, 6.5 Hz, 1H), 3.44 (dd, *J* = 10.4, 6.0 Hz, 1H), 5.00 (ddt, *J* = 15.2, 9.0, 1.4 Hz, 1H), 5.39 (dt, *J* = 15.2, 6.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7, 14.2, 16.0, 25.6, 29.1, 33.4, 38.8, 42.0, 69.1, 132.5, 133.1. HR-MS *m*/*z* calcd $[M+Na]^+$ for $C_{11}H_{22}ONa$ 193.1568, found 193.1554.

(36) Unfortunately, no optical rotation was reported for synthesized plakortone B, in ref 10.

(37) Rudi, A.; Kashman, Y. *J. Nat. Prod.* **1993**, *56*, 1827.

(5*R*,7*S*,*E*)-5-Ethyl-8-iodo-7-methyloct-3-ene (83): Yield 100%. $[\alpha]^{22}_D$ +2.3 (*c* 0.65, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 1.12−1.22 (m, 2H), 1.26−1.36 (m, 2H), 1.45−1.53 (m, 1H), 1.70−1.87 (m, 1H), 1.95−2.02 (m, 2H), 3.11 (dd, *J* = 9.5, 6.1 Hz, 1H), 3.17 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.00 (ddt, *J* = 15.2, 9.2, 1.8 Hz, 1H), 5.39 (dt, *J* = 15.3, 6.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.0, 14.4, 19.3, 20.2, 25.9, 29.1, 32.8, 42.5, 42.6, 133.0, 133.1. HR-MS (EI) *m*/*z* calcd for $C_{11}H_{21}I$ 280.0688, found 280.0684.

(3*S*,5*R*,*E*)-5-Ethyl-3-methylnon-6-enenitrile (84): Yield 79%. $[\alpha]^{22}_D$ +7.4 (*c* 0.7, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.6 Hz, 3H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 1.12−1.38 (m, 4H), 1.80−1.90 (m, 2H), 1.95−2.01 (m, 2H), 2.19 (dd, *J* = 16.5, 6.7 Hz, 1H), 2.25 (dd, *J* = 16.5, 6.1 Hz, 1H), 4.98 (ddt, *J* = 15.1, 9.1, 1.4 Hz, 1H), 5.40 (dt, *J* = 15.1, 6.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6, 14.1, 18.8, 25.5, 25.6, 28.2, 28.9, 30.9, 41.5, 42.2, 132.3, 133.2. HR-MS *m*/*z* calcd [M + Na] for $C_{12}H_{21}NNa$ 202.1572, found 202.1566.

(5*S*,7*R*,*E*)-7-Ethyl-5-methylundec-8-en-3-ol (86). The previous cyanide **84** was converted to the corresponding aldehyde following a literature procedure for a diastereomer[32] and the crude aldehyde was used for the next step without purification. To a cooled (−78 °C) solution of EtMgBr (3.0 M in ether, 4 mL) in dry THF (15 mL) was added dropwise a solution of crude aldehyde **85** (600 mg, 3.3 mmol) in THF (5 mL). Once the addition was completed, the solution was warmed gradually to rt and stirring was continued for another hour. After recooling to −10 °C, the solution was quenched by addition of saturated NH_4Cl. The aqueous layer was separated and extracted with DCM, followed by washing the combined organic extracts with brine and water. Drying ($MgSO_4$) and removal of the solvent afforded a crude residue, which was purified by flash chromatography (ether/hexane 1:4) to give 510 mg of the pure alcohol **86** (73%) as a diastereomeric mixture (40/60). ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.98−1.69 (m, 20H), 1.83−1.98 (m, 2H), 1.94−2.04 (m, 4H), 3.56−3.62 (m, 2H), 4.98−5.03 (m, 2H), 5.34−5.41 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ major isomer: 9.9, 11.7, 14.2, 18.8, 25.6, 26.7, 28.9, 30.8, 42.2, 43.6, 45.4, 71.0, 132.2, 133.3; minor isomer: 9.8, 11.8, 14.3, 20.2, 25.6, 26.9, 29.1, 30.4, 42.0, 43.6, 45.5, 71.0, 132.5, 133.3. HR-MS *m*/*z* calcd $[M + Na]^+$ for $C_{14}H_{28}ONa$ 235.2038, found 235.2032.

(5*S*,7*R*,*E*)-7-Ethyl-5-methylundec-8-en-3-one (87). To a solution of oxalyl chloride (0.45 mL, 5.3 mmol) in DCM (8 mL) at −78 °C was added dropwise DMSO (0.72 mL, 10.1 mmol). The resulting mixture was stirred at −78 °C for a further 5 min before adding dropwise a solution of alcohol **86** (0.5 g, 2.3 mmol) in DCM (5 mL). After the mixture was stirred at −78 °C for 1 h, an excess of triethylamine (2.2 mL, 15.6 mmol) was added and the solution was stirred for another 15 min. The solution was warmed to 0 °C for 20 min, followed by dilution with ether and washed with brine. After drying ($MgSO_4$), filtration, and concentration, the crude material was purified by flash chromatography (ether/hexane 1:9) to afford 345 mg of the pure ketone **87** (70%) as a colorless oil. $[\alpha]^{22}_D$ −10.0 (*c* 0.67, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.3 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 7.7 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H), 1.05−1.18 (m, 3H), 1.22−1.33 (m, 1H), 1.87−1.80 (m, 1H), 1.93−2.03 (m, 3H), 2.21 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.29 (dd, *J* = 15.5, 6.5 Hz, 1H), 2.36 (dq, *J* = 7.1, 1.0 Hz, 2H), 5.01 (ddt, *J* = 15.1, 9.2, 1.5 Hz, 1H), 5.38 (dt, *J* = 15.1, 6.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.8, 11.7, 14.2, 19.4, 25.6, 27.0, 28.9, 36.3, 42.1, 42.5, 50.9, 132.5, 132.9, 211.7. HR-MS *m*/*z* calcd $[M + Na]^+$ for $C_{14}H_{26}ONa$ 233.1881, found 233.1876.

(7*S*,9*R*,*E*)-5,9-Diethyl-5-hydroxy-7-methyltridec-10-en-3-one (88). At −78 °C, ^{n}BuLi (1.8 M in hexane, 2.2 mL) was added dropwise to 2-butanone *N*,*N*-dimethylhydrazone (537 mg, 4.7 mmol) in dry THF (25 mL) over 5 min under a nitrogen atmosphere. The reaction was stirred at −78 °C for 2 h, during which a white solid formed. Ketone **87** (330 mg, 1.57 mmol) in dry THF (4 mL) was then added dropwise and the solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the addition of 10% HCl (10 mL) and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was dissolved in THF (20 mL) and then added to $CuCl_2 \cdot 2H_2O$ (0.75 g, 4.4 mmol) in water (10 mL) and pH 7 phosphate buffer (5 mL). This mixture was stirred overnight at room temperature. The reaction was then quenched by the addition of aqueous NaCl−NaOH (pH 8, 20 mL) and was then extracted with DCM. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (ether/hexane 1:19) to afford the desired product **88** (184 mg, 41%) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (t, *J* = 7.4 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H), 0.821 (t, *J* = 7.6 Hz, 3H), 0.825 (t, *J* = 7.6 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 6H), 1.02 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H), 1.05−1.20 (m, 20H), 1.78−1.87 (m, 2H), 1.95−2.02 (m, 2H), 2.40−2.45 (m, 4H), 2.52−2.54 (m, 4H), 4.96−5.05 (m, 2H), 5.38 (dt, *J* = 15.2, 6.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.4 (2C), 8.3, 8.4, 11.7, 11.8, 14.23, 14.3, 21.1, 21.2, 25.6 (2C), 26.0 (2C), 28.98, 29.02, 32.1, 32.4, 37.9 (2C), 42.2, 42.3, 44.3, 44.7, 46.3, 46.4, 49.1, 49.2, 74.7, 74.8, 132.2, 132.3, 133.3, 133.4, 214.16, 214.20. HR-MS *m*/*z* calcd $[M + Na]^+$ for $C_{18}H_{34}O_2Na$ 305.2456, found 305.2451.

Plakortone C (90) and *epi*-Plakortone C (91). To a solution of hydroxy ketone **88** (184 mg, 0.65 mmol) in dry THF (10 mL) was added anhydrous $CeCl_3$ (690 mg, 3.15 mmol), and the mixture was stirred for 20 min. Vinylmagnesium bromide (1.65 M in THF, 1.90 mL) was added at room temperature and left to react for 1 h. AcOH (10%, 5 mL) was then added, and the solution was extracted with ether (3 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated to afford 180 mg of a colorless oil (90%). The crude **89** was immediately subjected to the hydroxycyclization−carbonylation−lactonization sequence following the general procedure, to give after workup the crude bicyclic lactones **90**−**93** in a 3:3:1:1 ratio. Flash chromatographic purification (ether/hexane 1:4) resulted in two fractions: 50 mg of a mixture of the major isomers **90** and **91** and 15 mg of a mixture of the 4 isomers **90**−**93** (33% in total over 2 steps). A fraction of the mixture of the major isomers (1:1) was subjected to HPLC (5% ethyl acetate in hexane, refractive index detector) for separation of the isomeric lactones and NMR analysis.

Synthetic plakortone C (90), identical to natural plakortone C (3). First eluted isomer, R_t 38 min. $[\alpha]^{22}_D$ −29.3 (*c* 0.47, $CHCl_3$). Reported[2] $[\alpha]^{22}_D$ −24.9 (*c* 1.23, $CHCl_3$). See Table 5 for ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$). HR-MS *m*/*z* calcd $[M + Na]^+$ for $C_{21}H_{36}NaO_3$ 359.2562, found 359.2557.

***epi*-Plakortone C (91).** Second eluted isomer, R_t 40 min. $[\alpha]^{22}_D$ +11.5 (*c* 0.7, $CHCl_3$). See Table 5 for ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$). HR-MS *m*/*z* calcd $[M + Na]^+$ for $C_{21}H_{36}O_3Na$ 359.2562, found 359.2558.

Plakortone F (94). A solution of synthetic plakortone C (**90**) (4.7 mg, 0.014 mmol) in hexane (2 mL) was stirred under a hydrogen atmosphere (1 atm) in the presence of a catalytic amount of Pd/C for 1 h. After filtration and concentration, the fully hydrogenated product, plakortone F (**94**), was obtained (4.2 mg, 90%) as a colorless oil. $[\alpha]^{22}_D$ −24.0 (*c* 0.40, $CHCl_3$). Reported[3] $[\alpha]^{22}_D$

−11.0 (*c* 0.001, $CHCl_3$). See Table 6 for ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$). HR-MS *m*/*z* calcd $[M + Na]^+$ for $C_{21}H_{38}O_3$ Na 361.2719, found 361.2713.

***epi*-plakortone F (95).** Following an identical procedure to that for **94**, *epi*-plakortone F (**95**) was obtained (4.8 mg, 80%) from *epi*-plakortone C (**91**) (6.0 mg, 0.015 mmol). $[\alpha]^{22}_D$ +3.4 (*c* 0.48, $CHCl_3$). See Table 6 for ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$). HR-MS *m*/*z* calcd $[M+Na]^+$ for $C_{21}H_{38}O_3$ Na 361.2719, found 361.2714.

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Supporting Information Available: Full experimental details for the synthesis of plakortones D (**4**) and E (**5**) as well as for (±)-dehydroplakortones D **105** and **106** and (±)-dihydroplakortone D **107**, copies of NMR spectra (^1H and ^{13}C) of new compounds and for **53**−**56**, **90**, **91**, **94**, and **95**, and crystallographic information files (CIF, ORTEP plot and crystal data) of the *p*-nitrobenzoate derivative of compound **42**. This material is available free of charge via the Internet at http://pubs.acs.org.