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Total Synthesis of *seco*-Plakortolide E and (−)-*ent*-Plakortolide I: Absolute Configurational Revision of Natural Plakortolide I

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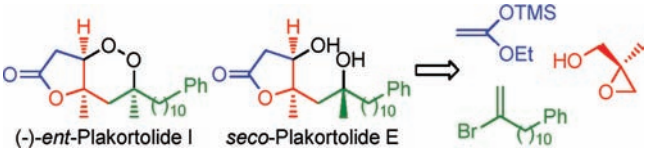
ABSTRACT



A first total synthesis of (−)-*ent*-plakortolide I and *seco*-plakortolide E was accomplished from (*S*)-2-methylglycidol. The relevant key reactions involve a diastereoselective Mukaiyama aldol reaction, a regioselective hydroperoxysilylation, and elaboration of the 1,2-dioxane ring by intramolecular Michael addition of a hydroperoxide group to a butenolide. This synthesis allowed the revision of the absolute configuration of plakortolide I and structural revision of plakortolide E.

Marine sponges of genus *Plakortis* and *Plakinastrella* are a prolific source of cyclic peroxides, with the majority possessing a 1,2-dioxan ring system.[1] Plakortolides are a family of secondary metabolites found in these sponges which have in common an aromatic unit connected via a methylene chain to a 4,6-dimethyl peroxylactone ring.[2] They differ in absolute configuration at C-3, C-4, C-6; the substitution pattern; the level of unsaturation; and the chain length. Plakortolide **1** was isolated from the extract of the Madagascar sponge *Plakortis aff. simplex*. The structure and relative configuration of **1** were established by NMR spectroscopic methods.[2g]

Its absolute configuration was determined by comparison of the optical rotation with that of its natural enantiomer, with the absolute stereochemistry established by application of Mosher's method to a MTPA derivative.[2d]

Crews and co-workers reported the isolation from Fidjian sponge *Plakortis sp.* of a new cytotoxic compound plakortolide E.[2c] Later on, Garson and co-workers found that NMR data reported for plakortolide E were inconsistent with its structure and are likely those of the corresponding *seco*-plakortolide E **2**.[2i]

Only one racemic synthesis of plakortolide I has been reported.[3] [4 + 2] Photocycloaddition of a singlet oxygen to a diene and iodolactonization are the keys steps for the construction of the peroxylactone framework of plakortolide I. A drawback of this strategy is the lack of stereochemical control at the newly formed stereogenic centers.

As a part of an ongoing project devoted to the directing effect of a double bond in the regiocontrol of intramolecular

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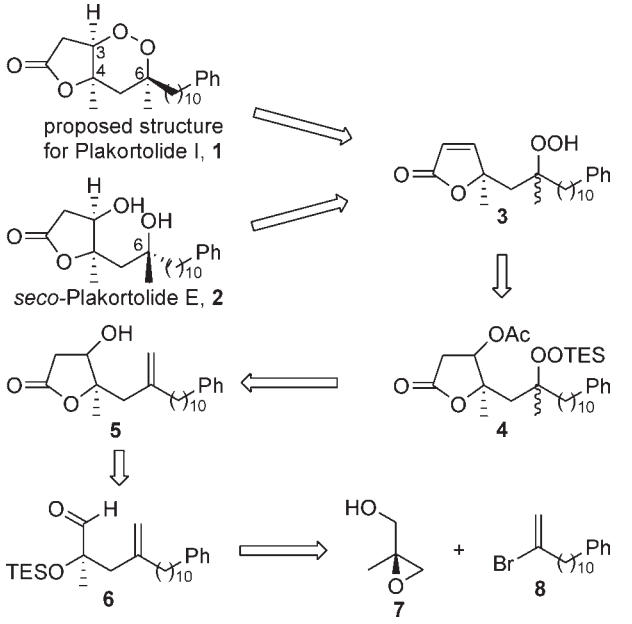
cyclization of hydroxyl vinyl epoxides,[4] we have recently reported a study concerning the application of this concept to forge 1,2-dioxane ring systems from β-hydroperoxy vinyl epoxides with the objective of synthesizing plakortolides. Unfortunately, the vinyl group had no directing effect on the regioselectivity of β-hydroperoxy vinyl *cis*-epoxide cyclization and exclusive formation of a 1,2-dioxolane was observed.[5] Consequently, a new synthetic route was elaborated for the construction of the 4,6-peroxylactone ring system of plakortolides.

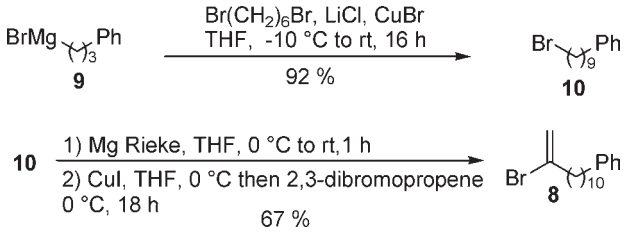
Herein we report the first total synthesis of (−)-*ent*-plakortolide I **1** and *seco*-plakortolide E **2** which differ in absolute stereochemistry only at C-6. In our retrosynthetic analysis we planned to install the 1,2-dioxane ring in the late stage of the synthesis because of its poor stability during functional group elaboration (Scheme 1).

Scheme 1. Retrosynthetic Analysis of Plakortolide I **1** and *seco*-Plakortolide E **2**



We envisioned that **1** and diol **2**, which is available by the O−O bond cleavage of its corresponding endoperoxide, could arise from a common intermediate **3** via an intramolecular Michael addition of a hydroperoxide group to a butenolide. As in our previous study of plakortolide synthesis,[5] we selected the regioselective hydroperoxysilylation of alkenes to introduce the peroxide functionality at C-6.[6] We have shown on a model butenolide bearing a 2-methylallyl substituent that the hydroperoxysilylation was not chemoselective; consequently the double bond of the butenolide moiety has to be protected during the installation of the hydroperoxide group.[7] We selected the oxotetrahydrofuranyl acetate as a mask form of butenolide because of the inertness of the acetate group in the peroxidation reaction conditions and easy dehydroacetylation in mild basic media. The masked butenolide **4** could originate from the protected hydroxyaldehyde **6** via a Mukaiyama aldol reaction with trimethysilyl ketene acetal and functional group manipulation. We believed that the protected homoallylic alcohol **6** could be prepared by Cu(I)- catalyzed addition of an organometallic derived from the vinyl bromide **8** to the known epoxide **7**.

Scheme 2. Synthesis of the Vinyl Bromide **8** from (3-Phenylpropyl)magnesium Bromide



We first prepared the fragment **8** from (3-phenylpropyl) magnesium bromide following the route in Scheme 2. Cu(I)-Catalyzed coupling between the Grignard reagent **9** and 1,6-dibromohexane (3 equiv) gave 9-phenylnonyl bromide **10** in excellent yield after its separation from the excess of 1,6-dibromohexane by fractional distillation.[8] A second coupling between (9-phenylnonyl)magnesium bromide[9] and 2,3-dibromopropene in excess led to the vinyl bromide **8** in moderate yield. We next focused our attention to the addition of organometallics derived from the bromide **8** to the protected 2-methylglycidol **12**, easily obtained in highly enantiomeric purity from 2-methallyl alcohol (Scheme 3).[10]

In the first experiment, heating of **8** and an excess of Mg for 30 min followed by addition, at low temperature, of a catalytic amount of CuI and epoxide **12** led to no detectable coupling product (Table 1, entry 1).

Conversely, the desired homoallylic alcohol **13** was obtained in fair yield by prolonged heating of the mixture of Mg and bromide **8** and by and increase of the reaction coupling time (Table 1, entry 2). The reaction conditions reported by Alexakis and co-workers, i.e. addition of the corresponding higher order cuprate of **8** to epoxide **12**, in the presence of $BF_3 \cdot Et_2O$, led to decomposition (entry 3).[11] Surprisingly, uncatalyzed addition of cuprate

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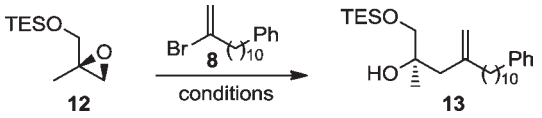
Table 1. Cu(I)-Catalyzed Addition of Organometallics Derived from Bromide **8** to Epoxide **12**



entry	conditions	yield of **13** (%)[a]
1	**8**, Mg (1.5 equiv), THF, Δ, 30 min then **12**, CuI, −40 to 0 °C, 2 h	–[b]
2	**8**, Mg (1.5 equiv), THF, Δ, 3 h then **12**, CuI, −30 to 0 °C, 18 h	52
3	**8**, *t*-BuLi (2.1 equiv), Et_2O, −78 °C, CuCN (0.5 equiv) then **12**, $BF_3 \cdot Et_2O$, −78° to 0 °C, 1 h	–[c]
4	**8**, *t*-BuLi (2.1 equiv), Et_2O, −78 °C, CuCN (0.5 equiv) then **12**, −25 to 0 °C, 1 h	**70**

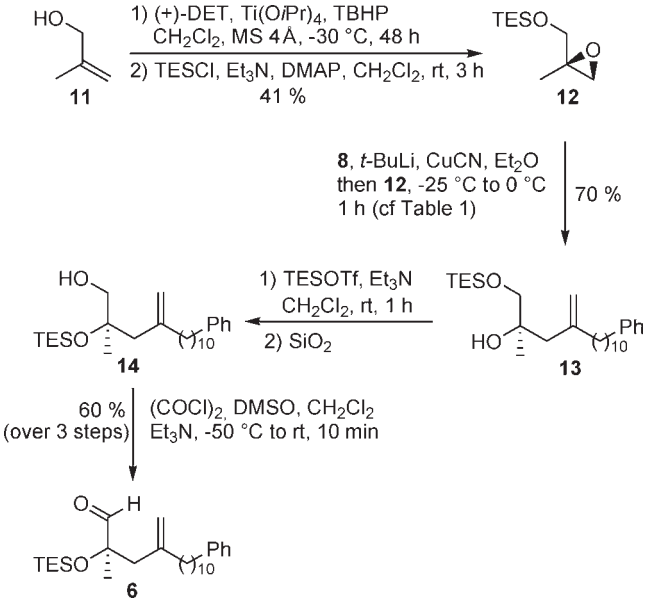
[a] Isolated yield. [b] No metal−bromine exchange was observed. [c] Decomposition.

derived from **8** to **12** afforded the tertiary alcohol **13** in good yield (entry 4).

Prior to the Mukaiyama aldol reaction, we had to transform the monoprotected diol **13** to the desired α- triethylsilyloxyaldehyde **6**. After protection of the tertiary alcohol within **13** as a TES ether, the resulting bis-TES ether was subjected to a selective oxidative deprotection under standard Swern conditions. Conversely to literature precedents, no reaction occurred.[12] Consequently, we adopted a stepwise method which consisted of selective deprotection of the primary TES ether with silica gel[13] followed by Swern oxidation to provide aldehyde **6** in 60% over three steps from **13**. With **6** in hand, the stage was set up for the Mukaiyama aldol addition. After some experimentation, we found that treatment of aldehyde **6** at −78 °C with [(1-ethoxyethenyl)oxy]trimethylsilane **15**, in the presence of $TiCl_2(OiPr)_2$,[14] led to the exclusive formation of the *syn*-adduct **16**[15] (Scheme 4).

Exposure of **16** to an excess of TBAF effected TMS and TES ether deprotection and subsequent lactonization. Acetylation of the resulting *β*-hydroxylactone furnished the acetate **17** in 59% yield over three steps to form **6**.

Scheme 3. Preparation of Key Aldehyde **6** from 2-Methallyl Alcohol



Regioselective hydroperoxysilylation of the disubstituted olefin within **17** accomplished by using $Co(thd)_2$,[16] in the presence of oxygen and triethylsilane, afforded the protected hydroperoxide in almost quantitative yield. Finally treatment of **4** at low temperature with DBU gave, via a three-step sequence, compounds **1** and **20** (58%) along with the intermediate **19** and the epoxyalcohol **18**. The formation of epoxide byproduct in the intramolecular Michael addition of the hydroperoxide groups is well-precedented.[17]

Exposure of **4** to DBU at 0 °C which effected *β*-elimination followed by successive addition of trifluoroethanol and TBAF minimized the epoxide formation providing **1** and **20** in 72% yield, separated by preparative TLC. Structures of **1** and **20** and their relative configurations were confirmed by 2D NMR experiments (HSQC, NOESY).

The synthetic sample of **1** was found to be identical in all respects to the natural product except for the sign of the optical rotation (Lit. values: $[\alpha]_D^{20}$ +8 (*c* 0.017, $CHCl_3$);[2g] for the enantiomer: $[\alpha]_D^{20}$ −8 (*c* 0.05, $CHCl_3$);[2d] observed: $[\alpha]_D^{20}$ −9 (*c* 0.7, $CHCl_3$). Since our synthetic route from (*S*)-2-methylglycidol was unambiguous, Kashman and coworkers misassigned the absolute configuration of plakortolide I. Thus, the revised absolute configuration of plakortolide I is 3*S*, 4*S*, 6*R*.

In order to confirm Garson's assumption that the structure of "plakortolide E" was in fact that of its corresponding

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(14) For an example of $TiCl_2(OiPr)_2$-catalyzed Mukaiyama Aldol reaction with trimethysilyl ketene acetal, see: Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.—Eur. J.* **2006**, *12*, 1185–1204.

(15) The relative stereochemistry of **16** was determined by 2D NMR techniques after its transformation to the lactone **17**.

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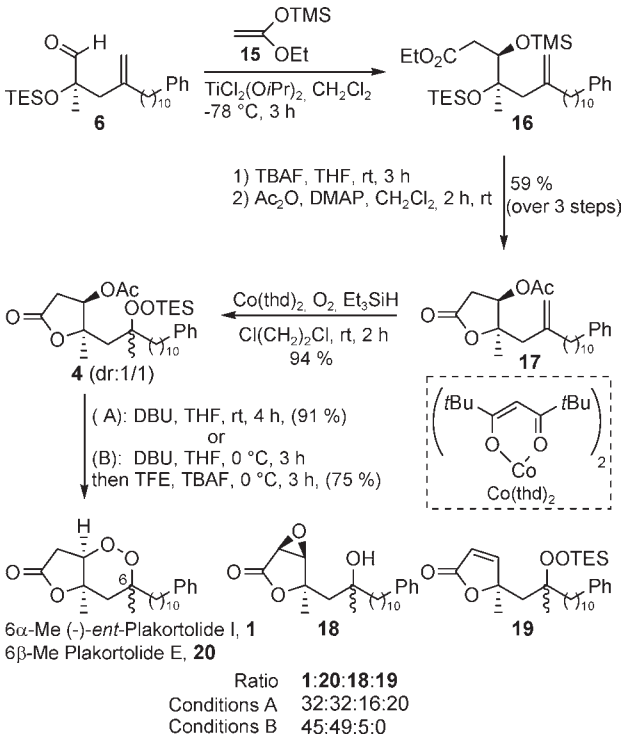
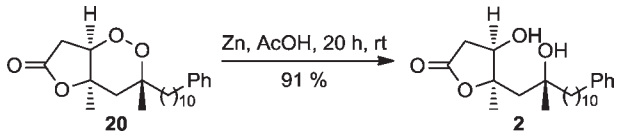
Scheme 4. Completion of the Synthesis of Plakortolides I and E from Aldehyde **6**



seco-plakortolide **2**, the peroxy ring of **20** was reductively cleaved, using Zn/AcOH, to afford **2** in excellent yield (Scheme 5).

Scheme 5. Reductive Cleavage of the Peroxy Ring of **20**



NMR data of synthetic **2** were in perfect agreement with those of "plakortolide E" reported by Crews and coworkers as well as its specific rotation ($[\alpha]_D^{20}$ +7.7 (*c* 0.15, $CHCl_3$); Lit.[2c] $[\alpha]_D^{20}$ +10 (*c* 0.09, $CHCl_3$)).

In conclusion, we have achieved the first total synthesis of the natural *ent*-plakortolide I **1** and *seco*-plakortolide E **2** leading to the structural revision for plakortolide E to structure **2** and revision of the absolute configuration of **1**. The use of the regioselective hydroperoxysilylation of a *gem*-disubstituted olefin coupled to a high-yielding Mukaiyama aldol reaction allowed rapid construction of the peroxylactone core of plakortolides. Synthesis of **1** and **2** comprises respectively 11 and 12 steps starting from 2-methallyl alcohol with 3.5% and 3.3% overall yields.

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