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Absolute Configuration of Methyl (2*Z*,6*R*,8*R*,9*E*)-3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate from the Sponge *Plakortis halichondrioides*

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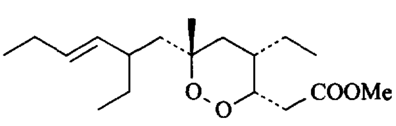
Abstract: The absolute stereochemistry of methyl ester **2**, which is a major metabolite of the Caribbean sponge *Plakortis halichondrioides*, was determined to be 6*R*,8*R* by means of chemical degradation and application of a modification of Mosher's method. The absolute configuration at C-8 was determined by analysis of the ^{1}H NMR spectra of the amides formed from the acid **4** and (*R*)- and (*S*)-phenylglycine methyl ester.

Although advances in NMR technology have greatly simplified the structural elucidation of natural products, it is still difficult to determine the stereochemistry of certain classes of compounds. Foremost among these problems is the determination of the absolute configuration at centers where an alkyl group is attached to a longer alkyl chain. In this paper we present a solution to this problem which can be applied in situations where the alkyl group is allylic.

The earliest reports of cyclic peroxides from sponges, exemplified by the isolation of plakortin (**1**) from the Caribbean sponge *Plakortis halichondrioides*,[1] contained limited stereochemical assignments.[2] In recent years, some progress has been made in reliably deducing the relative[3] and absolute[4] stereochemistry of stereocenters around the peroxide ring, but the problem of assigning the stereochemistry of the side-chain remained. Our interest in this problem arose from an inquiry[5] about the enantiomeric integrity of the methyl ester **2** that we had earlier isolated from a specimen of *P. halichondrioides*.[6]



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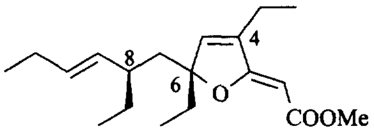

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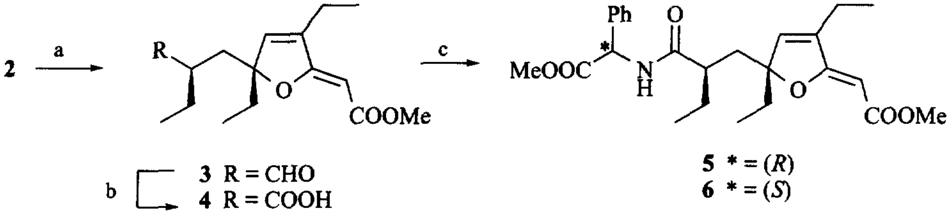
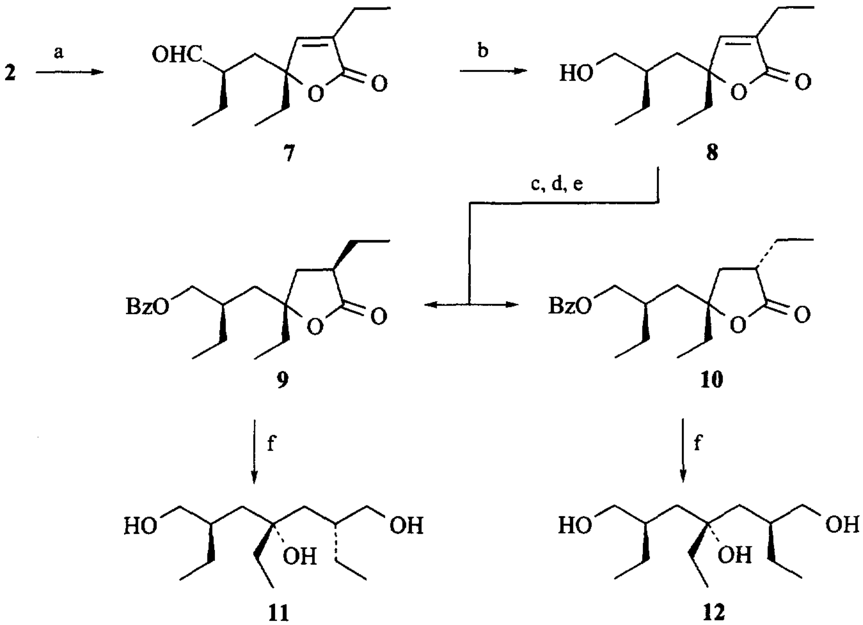
Our strategy for assigning the absolute stereochemistry of methyl ester **2** was to first determine the absolute configuration at C-8 and then elucidate the relative stereochemistry at C-6. The latter process is particularly difficult because there are no other chiral centers on the dihydrofuran ring, but the problem can be attacked by hydrogenation of the 4,5-double bond to create an asymmetric center at C-4, which then allows the stereochemistry at C-4 and C-6 to be related. In cyclic peroxides such as plakortin (**1**), the absolute and relative stereochemistry about the peroxide ring can readily be determined, thus making the procedure described below of general application to the structural determination of cyclic peroxides in this series.

A sample of the methyl ester **2**, $[\alpha]_D = -175°$ (c 1.4, CCl_4), that had been stored at 4°C for 16 years was shown to be essentially pure by HPLC.[7] Analysis of the ^{1}H NMR data, particularly the NOEDS data, revealed that the compound was unchanged but that the stereochemistry of the 2,3-double bond had been incorrectly assigned in 1980 on the basis of the chemical shift of H-2. Careful ozonolysis of the methyl ester **2**, followed by oxidation of the resulting aldehyde **3** with sodium chlorate, gave the corresponding acid in 66% overall yield (Scheme 1).[8] The absolute stereochemistry at C-8 was determined by application of the chiral amide method developed by Nagai and Kusumi,[9] in which the acid **4** was reacted with (*R*)- and (*S*)-phenylglycine methyl ester (PGME) and the ^{1}H NMR spectra of the resulting amides **5** and **6** were compared (Table 1). The NMR analysis indicated that no racemization had occurred during the oxidation procedure and that the absolute configuration at C-8 was *R*.



Scheme 1. a. O_3 (5% in Ar), EtOAc, 1 hr., -78°; then DMS (excess) (95%). b. $NaClO_2$, PO_4^{2-} buffer (pH 7), 2-methyl-2-butene, 24 hrs, 4°C (70%). c. (*R*)- or (*S*)-PGME, benzotriazolyloxytri(pyrrolidinyl)-phosphonium hexafluorophosphate (PyBoP) (1.5 eq.), 1-hydroxybenzotriazole (HOBT) (1.5 eq), N-methylmorpholine (cat.), 4 hr. (90%).



Scheme 2. a. OsO_4 (cat.), $NaIO_4$, 24 hr. (90%). b. $NaBH_4$ (excess), MeOH, 15 min.. c. H_2, Pd-C (4 mol%), MeOH, 3 hrs. d. BzCl (1.5 eq.), TEA (1.5 eq.), DMAP (cat.), DCM, 15 min. e. Silica gel HPLC (25% for b-e). f. $LiBH_4$ (excess), MeOH (1.5 eq.), Et_2O, 1 hr., reflux (95%).

Oxidation of methyl ester **2** with osmium tetroxide/sodium periodate produced the lactone **7** containing an aldehyde at C-9 that was reduced with sodium borohydride to the alcohol **8** (Scheme 2). Hydrogenation of the olefin gave a 55:45 mixture of diastereoisomers at C-2 that could be readily separated by HPLC on silica as the corresponding benzoyl esters **9** and **10**. The relative stereochemistry about the five-membered ring was determined using NOEDS experiments to be *cis*-diethyl for **9** and *trans*-diethyl for **10**. Reduction of the HPLC-pure lactones **9** and **10** with lithium borohydride[10] resulted in the formation of triols **11** and **12**, respectively. The relative and hence absolute stereochemistries of the triols **11** and **12** were immediately apparent from examination of the ^{1}H NMR spectra (Figure 1): the C_s symmetry of triol **12** resulted in a relatively simple spectrum compared with the more complex spectrum of the unsymmetrical triol **11**.[11] Thus, the methyl ester **2** is defined as methyl (2*Z*,6*R*,8*R*,9*E*)-3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate.

Table 1. 500 MHz ^{1}H NMR data for the (*R*)- and (*S*)-PGME amides of 7 in $CDCl_3$.

H#	δ_S	δ_R	$\Delta\delta_{(S-R)}$
2	4.63 (s)	4.82 (s)	-0.19
5	6.02 (s)	6.29 (s)	-0.27
7	1.86 (m), 2.33 (m)	1.86 (m), 2.30 (m)	0, +0.03
8	1.99 (br m)	1.99 (br m)	0
9	1.58 (m), 1.82 (m)	1.38 (m), 1.47 (m)	+0.20, +0.35
10	0.85 (t, J = 7)	0.69 (t, J = 7)	+0.16
12	1.55 (m)	2.10 (m)	-0.55
13	0.86 (t, J = 7)	1.08 (t, J = 7)	-0.22
14	1.68 (m), 1.78 (m)	1.72 (m), 1.82 (m)	-0.04, -0.04
15	0.71 (t, J = 7)	0.76 (t, J = 7)	-0.05
16	3.66 (s)	3.69 (s)	-0.03

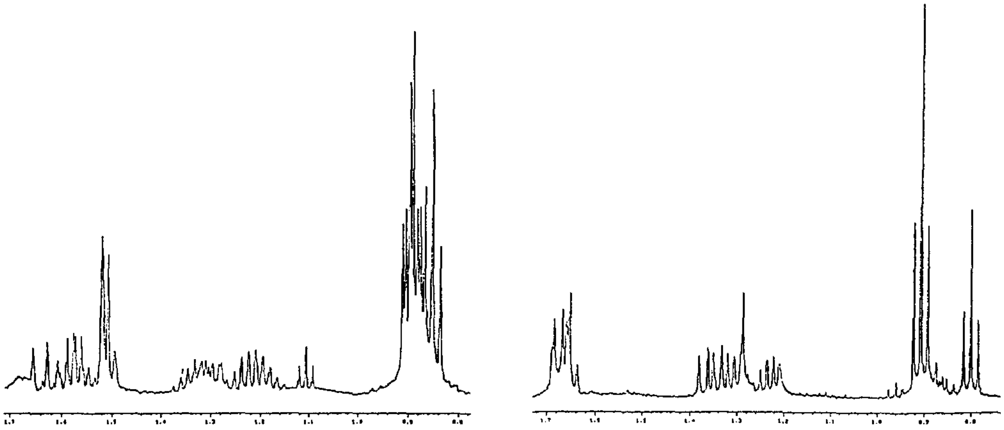


Figure 1. Comparative upfield regions of ^{1}H NMR spectra of **11** (left) and **12** in acetone-d_6.

References and notes

1. Higgs, M.D.; Faulkner, D.J. *J. Org. Chem.* **1978**, *43*, 3454.

2. Faulkner, D.J. *Nat. Prod. Rep.* **1984**, *1*, 513 and subsequent reports in this series.

3. a) De Guzman, F.S.; Schmitz, F.J. *J. Nat. Prod.* **1990**, *53*, 926. b) Patil, A.D.; Freyer, A.J.; Carte, B.; Johnson, R.K.; Lahouratate, P. *J. Nat. Prod.* **1996**, *59*, 219. Relative stereochemistry was determined by NOE experiments.

4. a) Kobayashi, M.; Kondo, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 1324. This work, using Mosher's method, represents the first assignment of absolute configuration in this class of compounds. b) Varoglu, M.; Peters, B.M.; Crews, P. *J. Nat. Prod.* **1995**, *58*, 27.

5. We thank Dr. Ying-cai Peng of Zhongshan University, People's Republic of China, for bringing this problem to our attention and for proposing the revision of the double bond geometry at C-2.

6. Stierle, D.B.; Faulkner, D.J. *J. Org. Chem.* **1980**, *45*, 3396. The sign of the optical rotation of methyl ester **2** ($[\alpha]_D = -175°$) was incorrectly reported.

7. The sample had become a very pale yellow during storage.

8. All key intermediates were purified by HPLC and were fully characterized by ^1H NMR, HRMS, IR, and UV. NOESY, COSY, and ^{13}C data were used to further substantiate several structures.

9. Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853.

10. Soai, K.; Okawa, A.J. *J. Org. Chem.* **1986**, 51, 4000.

11. ^{13}C spectral data also confirmed the stereochemical assignments.

12. We thank Dr. Jay S. Siegel (University of California, San Diego) for helpful comments on this manuscript. The ester **2** was originally isolated in our laboratory by Donald B. Stierle. This work was supported by the California Sea Grant College Program (NOAA grant NA36RG0537, project R/MP-60).

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