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SYNTHESIS IN THE PLAKORTONE SERIES: PLAKORTONE E

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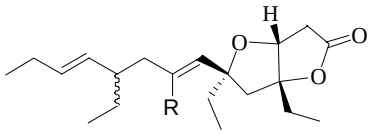
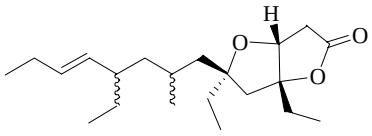
Abstract– A Pd(II)-mediated hydroxycyclisation-carbonylation-lactonisation sequence has operated efficiently with racemic enediol (**8**) to furnish (four) separable diastereomers of the bicyclic lactone system assigned to the sponge-derived, bioactive plakortone E. All four are *cis* ring-fused, and one is identical, on the basis of ^{1}H and ^{13}C NMR spectroscopic comparisons, with plakortone E, thus confirming its constitution and relative stereochemistry about the bicyclic lactone core. This synthetic approach, when applied to stereoisomer (**13**), will establish the absolute stereochemistry of plakortone E, likely to be that shown for (**14**).

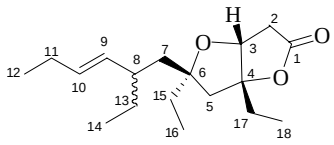
A variety of bioactive, oxygenated polyketide metabolites have been isolated from sponges of the genus *Plakortis*, and peroxides and lactones are prominent in this regard.[1] Of special interest are the plakortones, a family of bicyclic lactones, some members of which constitute a new class of activators of cardiac SR-Ca^{2+}-pumping ATPase, as well as exhibiting cytotoxic activity.[2,3] Six members, plakortones **A**-**F**, have so far been isolated and are shown in Figure 1.



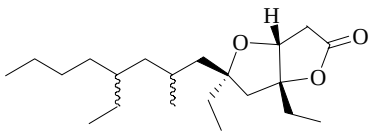
Plakortones **A** (R =Et), **B** (R = Me)



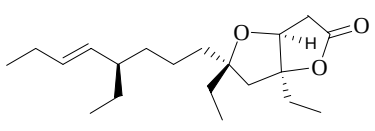
Plakortones **C** (R = Me), **D** (R = H)



Plakortone **E**



Plakortone **F**



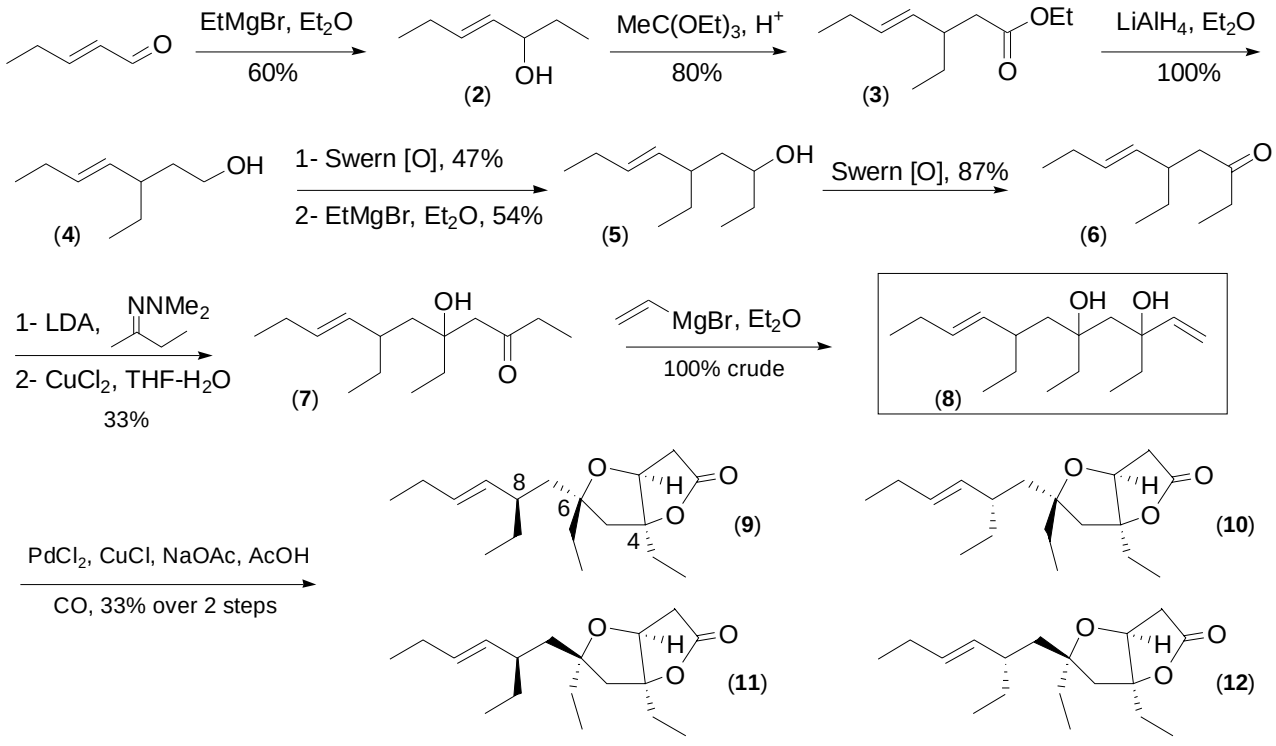
(**1**)

Absolute Stereochemistry of Plakortone D

Figure 1

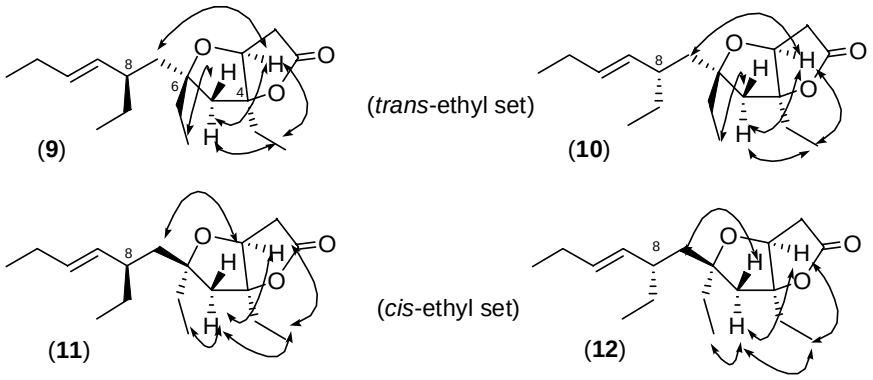
The total synthesis of plakortone **D**[4] has confirmed its structure and absolute stereochemistry as (**1**), and this stereochemistry is likely to characterize plakortones **A**, **B** and **C** as well. Plakortones **E** and **F** were isolated more recently[3] and provide additional side-chain variety in the family members. Plakortone **E** has a shortened side chain (by 2 carbons), whereas plakortone **F** is the fully saturated relative of plakortone **B**. Plakortones **B**, **C**, **D**, **E** and **F** all exhibit cytotoxic activity, with plakortone **E** being the most active. The relative stereochemistry (for plakortone **E**) about the bicyclic system was based on a 2D ROESY spectrum,[3] but that at the ethyl bearing C-8 was not defined. In view of the structural novelty and bioactivity of plakortone **E**, we have undertaken additional synthetic work that confirms its structure and likely stereochemistry.

The synthetic scheme adopted for acquisition of the four, racemic *cis*-fused diastereomers of plakortone **E** bears some resemblance to that employed for the total synthesis of plakortone **D**.[4] In that approach,[4] the bicyclic lactone core was first constructed using a Pd(II)-mediated hydroxycyclisation-carbonylation-lactonisation cascade. The oxidation level of the pendant hydroxymethyl group was adjusted to the aldehyde level, and then coupled with an independently generated, sulfone activated, side chain unit. In the present work, the required complete acyclic carbon skeleton[5] was assembled first, and then transformed to plakortone **E**, again using the Pd(II)-mediated procedure. The required dienediol (**8**) was accessed as shown in Scheme 1.



Scheme 1: Synthesis of Diastereomers of Plakortone E (Stereostructures (**9**)-(**12**) indicate relative stereochemistry)

It was pleasing that the final carbonylation lactonisation step proceeded satisfactorily on a more complex dienediol system (**8**),[6] to afford diastereomers (**9**), (**10**), (**11**), and (**12**), which are separable by HPLC. Detailed NMR spectral examinations, in particular NOESY spectra, permitted the four isomers to be grouped into two sets of two, on the basis of the *cis* or *trans* relationship of the ethyl groups at C-4 and C-6. These pairings are shown below, with the important NOE's indicated. (It was not possible to relate unambiguously, the stereochemistry at C-8 to that of the bicyclic system).



A full listing of the ^{13}C and ^{1}H NMR spectral data (500 MHz, $CDCl_3$) for the four synthesized isomers,[7] and plakortone **E**, are shown in Tables 1 and 2. (The reported ^{13}C NMR shift for C-8 (45.3 ppm) in plakortone E has been corrected to δ 40.7).[8] There are sufficient variations in the ^{13}C and ^{1}H NMR spectral data between (natural) plakortone E and the four synthetic isomers to establish that the second eluting isomer (HPLC2), is identical with the natural compound.

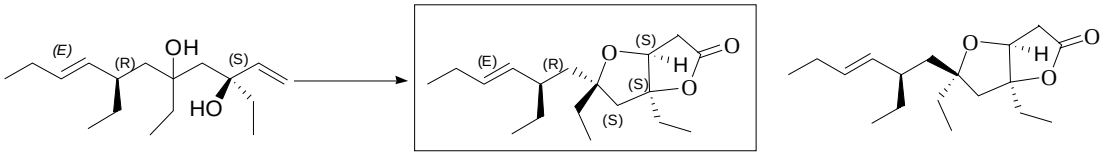
	Plakortone E	HPLC1	HPLC2	HPLC3	HPLC4
		[*trans*-ethyl set, (**9**) or (**10**)]		[*cis*-ethyl set, (**11**) or (**12**)]	
1	175.5	175.6	175.6	175.5	175.6
2	37.5	37.6	37.5	37.3	37.4
3	80.2	80.8	80.0	79.9	79.5
4	98.0	97.9	97.9	97.9	98.1
5	46.2	44.6	46.0	45.4	47.2
6	88.2	87.7	87.7	87.5	87.3
7	43.6	43.4	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	29.6	30.0	29.7	29.9	29.7
14	11.7	11.6	11.6	11.6	11.6
15	31.7	32.8	31.7	31.4	30.5
16	8.4	8.5	8.3	8.1	7.9
17	30.5	30.2	30.4	30.5	30.4
18	8.5	8.6	8.6	8.5	8.5

Table 1: ^{13}C NMR spectral data comparisons between natural plakortone **E** and synthetic diastereomers

	Plakortone E	HPLC1	HPLC2	HPLC3	HPLC4
		[*trans*-ethyl set, (**9**) and (**10**)]		[*cis*-ethyl set, (**11**) and (**12**)]	
1					
2	2.7, 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
4					
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
6					
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, 7.5,1.5	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	1.40, 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
14	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
15	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			
16	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
17	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	
18	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

Table 2: ^{1}H NMR spectral data comparisons between natural plakortone **E** and synthetic diastereomers

The present report confirms the constitution of plakortone E,[3] and the relative stereochemistry about the bicyclic lactone core. In addition, the Pd(II)-mediated hydroxycyclisation-carbonylation-lactonisation cascade operates efficiently with the racemic dienediol (**8**), and this approach is the basis for an enantioselective synthesis commencing with (**13**) which will establish the absolute stereochemistry of plakortone E.



(**13**) (**14**) (**15**)

In this connection, we are mindful that each of the plakortones **A-F** is levorotatory[2,3] and as we have demonstrated that plakortone **D** possesses the (3*S*, 4*S*, 6*S*, 10*R*, 11*E*) configuration,[4] plakortone **E** is likely to possess the boxed configuration (**14**). This isomer along with the separable (**15**) would form from the dienediol (**13**). These endeavors will be reported in full at a later date.

ACKNOWLEDGEMENTS

This research was supported by the Australian Research Council, to whom we are grateful.

REFERENCES

1. See, for example, D. B. Stierle and D. J. Faulkner, *J. Org. Chem.*, 1980, **45**, 3396.
2. A. D. Patil, A. J. Freyer, M. F. Bean, B. K. Carte, J. W. Westley, R. K. Johnson, and P. Lahouratate, *Tetrahedron*, 1996, **52**, 377.
3. F. Caffierei, E. Fattorusso, O. Taglialatela-Scarfati, M. Di Rosa, and A. Ianaro, *Tetrahedron*, 1999, **55,** 13831.
4. P. Y. Hayes and W. Kitching, *J. Am. Chem. Soc.*, 2002, **124**, 9718.
5. It is of interest that in an overlooked study of the sponge *Plakortis halichondrioides*, Rudi and Kashman (A. Rudi and Y. Kashman, *J. Nat. Prod.*, 1993, **56**, 1827) characterized, among other compounds, C-8 alkylated (methyl, ethyl) acids such as 4,6-dihydroxy-4,6,8,10-tetraethyl-tetradec-2,7,11-trienoic acid, but no plakortone structures. However, an acid-catalysed cyclisation-lactonisation sequence of this acid would provide plakortone A.
6. Dienediol (**8**) was employed directly, without purification. Its immediate precursor, ketol (**7**) was fully characterized: **GCMS** (m/z): 222 ($M^{+\cdot} - H_2O$), 211 ($M^{+\cdot}$ – Et). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.783 (t, 7.5, 3H), 0.785 (t, 7.5, 3H), 0.82 (t, 7.5, 3H), 0.84 (t, 7.5, 3H), 0.93 (t, 7.5, 3H), 0.95 (t, 7.5, 3H), 1.01 (t, 7.5, 3H), 1.16-1.20 (m, 2H), 1.32-1.40 (m, 2H), 1.42-1.61 (m, 8H), 1.95-2.00 (m, 6H), 2.37 (q, J 7.4, 2H), 2.44 (q, 7.4, 2H), 2.52 (d, 15.0, 1H), 2.53 (d, 15.0, 1H), 2.58 (d, 15.0, 1H), 2.65 (d, 15.0, 1H), 3.31 (br s, 1H, OH), 3.73 (br s, 1H, OH), 5.07 (ddt, 15.3, 9.3, 1.5, 1H), 5.13 (ddt, 15.3, 9.3, 1.5, 1H), 5.40 (dt, 15.3, 6.3, 1H), 5.42 (dt, 15.3, 6.3, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ *Minor isomer (40%)* 7.5, 8.2, 11.5, 13.9, 25.5, 29.9, 32.7, 37.9, 40.4, 43.7, 49.6, 74.7, 132.6, 134.7, 213.1. *Major isomer (60%)*: 7.4, 7.6, 11.5, 13.9, 25.6, 30.0, 31.8, 37.6, 40.8, 43.6, 49.8, 74.2, 132.4, 134.7, 213.5. **HRMS** (70 eV): Calcd for $C_{15}H_{28}O_2Na$ ($M^{+\cdot}$ + Na): 263.1987. Found: 263.1984.
7. **GCMS** (m/z): 265 ($M^{+\cdot}$ – Et), 183, 169, 109, 97, 57, 55. **HRMS** (70 eV): Calcd for $C_{18}H_{30}O_3Na$ ($M^{+\cdot}$ + Na): 317.2092. Found: 317.2092.
8. We are grateful to Professor Fattorusso (Naples) for exchanges of spectra and information on this point. The ^{13}C NMR spectral data for plakortone E in Table 1 are derived from the HSQC spectrum provided by Professor Fattorusso.