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Total synthesis and absolute stereochemistry of plakortone E

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Abstract—The absolute stereochemistry of plakortone E, a cytotoxic metabolite of the Caribbean sponge, was established to be **1**, by the synthesis of the racemic C-8 epimer (±)-**2** and then of (−)-**1** itself, which was identical with the natural compound.

Plakortones, poliketide metabolites of marine sponges of the genus *Plakortis*, show interesting biological activities.[1] Plakortones A–D are activators of cardiac sarcoplasmic reticulum Ca^{2+} pumping ATPase[1a] and plakortones B–G exhibit in vitro cytotoxicity on tumor cell lines (Fig. 1).[1b,c] The relative configurations of the core moiety in plakortones A–F were determined to be common by NOE analysis, however, the stereochemistries of the side chain in many plakortones are still unknown. Absolute configurations of plakortones D[2] and G[3] were determined, respectively by total syntheses.[2,3] The configuration of a quaternary center in plakortone G is the opposite of that of the corresponding center in plakortone D. On the other hand, the core part of the other bicyclic plakortones (A, B, C, E, F) was speculated to have the same configuration as plakortone D, based on these levorotatory characters.[2]

(−)-Plakortone E, which exhibits high cytotoxicity on a murine fibrosarcoma cell line, was isolated from *Plakortis simplex* in 1999.[1b] Lactones **1** and **2** were synthesized in racemic form by the Kitching group and the NMR spectra of one of the two diastereomers were identical with those of plakortone E. Although the relative stereochemistry of the core part of them was clear, the stereochemistry between C-6 and C-8 was ambiguous.[4a] It was presumed that the absolute structure **1** is likely for plakortone E by analogy with plakortone D,[4a] however, precise evidence has not yet been found. This correspondence, however, is confirmed by the present work.

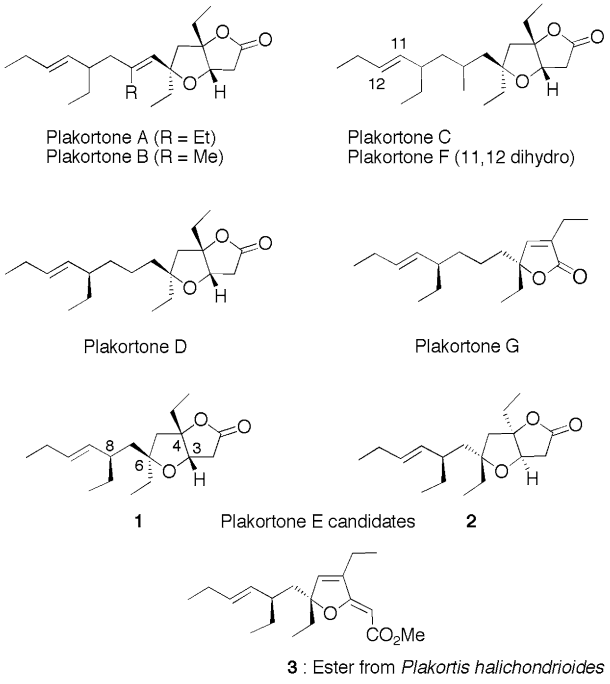

Figure 1.

Recently, we completed the stereocontrolled synthesis of (±)-methyl-3,6-epoxy-4,6,8-triethyl-2,4,9-dodecatrienoate (**3**),[5] which has the same carbon framework as

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plakortone E. The absolute stereochemistry of **3** had been determined as shown by chemical degradation.[6] Considering the possibility that stereochemistries at C-6 and C-8 of plakortone E are the same as those of ester **3**, we started the synthesis of (±)-**2** from the synthetic intermediate of (±)-**3**. The relationship between C-6 and C-8 of (±)-**2** should become clear with our strategy.

After some model studies, we carried out iodolactonization of **4** to give iodide **5** under various conditions. The yield was, however, less than 30% due to lability of the double bond in the side chain. Also unfortunately, attempted reduction of iodide **5** with Bu_3SnH gave the tricyclic compound **6** (Fig. 2). Thus, we turned to the modified route where the double bond was introduced at the final stage.

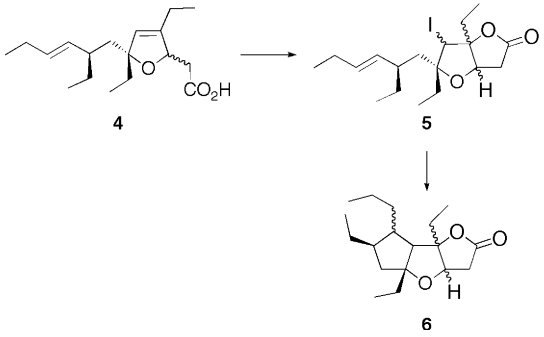
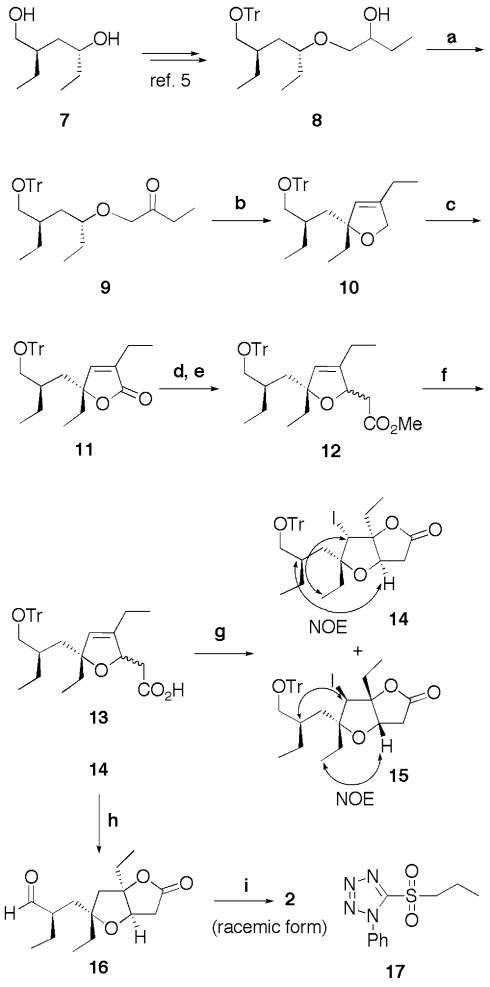


Figure 2.

Alcohol **8**, derived from the racemic diol **7**,[5] was oxidized with IBX to ketone **9** (Scheme 1). The reaction between lithiotrimethylsilyldiazomethane ($TMSCLiN_2$)[7] and **9** in THF afforded dihydrofurane **10** in good yield via C–H insertion reaction of the alkylidenecarbene. Allylic oxidation of **10** with PCC was unsuccessful due to instability of the trityl group, however, the use of CrO_3 and 3,5-dimethyl pyrazole in CH_2Cl_2 at −20 °C produced lactone **11** cleanly. Reduction of **11** with DIBAL followed by treatment of the resultant hemiacetal with methyl(triphenylphosphoranylidene)acetate gave methyl ester **12** as a 1:1 mixture of diastereomers. Without separation, ester **12** was subjected to alkaline hydrolysis and subsequent iodolactonization to provide bicyclic lactones **14** and **15** in good yield as readily separable diastereomers. The stereochemistries of both compounds were determined by NOE experiments. Lactone **14**, with the desired stereochemistry at the core moiety, was exposed to Bu_3SnH and AIBN in benzene. It was delightful for us to find the product was aldehyde **16** instead of the expected iodine-free trityl ether. The oxidoreductive reaction is rationalized by radical generation on the tetrahydrofuran ring followed by 1,5 hydrogen transfer and elimination of the trityl radical (Fig. 3).[8] The diastereomer **15** also gave the corresponding aldehyde under the same conditions.

Aldehyde **16** was coupled with the anion generated from the sulfone **17**[9] to afford the final product (±)-**2**[10] accompanied by the *Z* isomer (10:1 ratio). The ^1H and ^{13}C NMR spectra of the synthetic sample of (±)-**2** were



Scheme 1. Reagents and conditions: (a) IBX, Py, DMSO, 45 °C (97%); (b) $TMSCHN_2$, BuLi, THF, −78 to 0 °C (81%); (c) CrO_3, 3,5-dimethyl pyrazole, CH_2Cl_2, −20 °C (75%); (d) DIBAL, CH_2Cl_2, −78 °C; (e) $Ph_3PCHCO_2CH_3$, PhMe, reflux (72% in two steps); (f) LiOH, EtOH–H_2O, rt (94%); (g) I_2, $NaHCO_3$, CH_2Cl_2–H_2O, rt (94%); (h) Bu_3SnH, AIBN, C_6H_6, reflux; (i) **17**, KHMDS, THF, −78 °C to rt (60% in two steps).

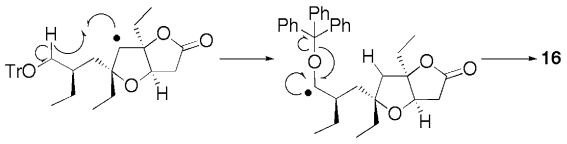
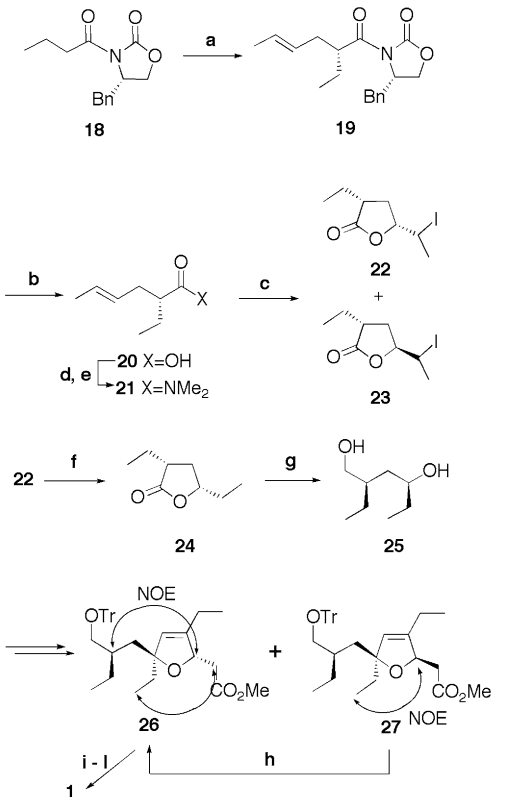


Figure 3.

not identical with those of the natural product,[1b] but identical with those of another epimer synthesized by the Kitching group.[4a]

Now the relative stereochemistry of plakortone E must be as shown in structure **1**. Accordingly, we immediately set about the synthesis of **1** in an optically active form.

The Evans asymmetric alkylation of the chiral imide **18** with crotyl bromide provided olefin **19**[11] with 99.9% de



Scheme 2. Reagents and conditions: (a) LDA, crotyl bromide, HMPA, THF, −78 °C (94%); (b) 30% H_2O_2, LiOH, THF–H_2O, rt (92%); (c) I_2, $NaHCO_3$, CH_2Cl_2–H_2O, rt (93%); (d) PivCl, Et_3N, THF, −10 °C to rt; (e) Me_2NH–HCl, Et_3N, CH_2Cl_2, rt (91% in two steps); (f) Bu_3SnH, AIBN, C_6H_6, reflux (quant.); (g) $LiAlH_4$, THF, 0 °C (92%); (h) DBU, PhMe, reflux (quant.); (i) LiOH, EtOH–H_2O, rt (85%); (j) I_2, $NaHCO_3$, CH_3CN, rt (90%); (k) Bu_3SnH, AIBN, C_6H_6, reflux; (l) **17**, KHMDS, THF, −78 °C to rt (69% in two steps).

(Scheme 2). Removal of the chiral auxiliary with lithium hydroperoxide gave carboxylic acid **20**. Iodolactonization of **20** produced lactones **22** and **23** in a 2:1 ratio. Under similar conditions, amide **21** gave the iodo lactones with the reversed selectivity (**22**:**23** = 1:10).[12] Iodide **22** was separated and reduced to lactone **24**, which was treated with $LiAlH_4$ to give diol **25**. Direct reduction of iodide **22** with $LiAlH_4$ to diol **25** was possible, however, a partial (ca. 10%) epimerization occurred probably via the elimination of HI from iodide **22**. Along the reaction sequence from **7** to **12**, diol **25** was converted into a 1:1 mixture of methyl esters **26** and **27**. Those diastereomers were separated at this stage by silica gel column chromatography, and the stereochemistry of **26** was determined by NOE experiment to be the desired one. When ester **27** was heated with DBU in toluene, it epimerized to a mixture of **26** and **27** through β-elimination and Michael addition. Thus, undesired ester **27** was convertible to **26** by repeated epimerization–separation sequence. Finally, ester **26** was transformed to the target compound (−)-**1**[13] in four steps. The optical rotation and the ^1H and ^{13}C NMR spectra of the synthetic sample of (−)-**1** were identical with those of the natural product. The absolute stereochemistry of plakortone E was thus determined to be (3*S*,4*S*,6*S*,8*R*) as previously suggested.[2,4a]

Additionally, the optically active diol **7**, which was obtained from **23** was converted to (−)-**3** in the same way as racemate.[5] The sign of the optical rotation of synthetic (−)-**3** was identical with that of the natural product, therefore, the absolute structure of (−)-**3** was confirmed.[14] It is notable that the stereochemical relationship of (−)-**1** and (−)-**3** is the same as that of plakortone D and plakortone G.

In summary, we determined the relative stereochemistry of plakortone E by the synthesis of its racemic C-8 epimer and confirmed the absolute configuration by its own enantioselective synthesis.

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10. ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, 3H, $J = 7.4$ Hz), 0.84 (t, 3H, $J = 7.4$ Hz), 0.97 (t, 3H, $J = 7.4$ Hz), 1.01 (t, 3H, $J = 7.4$ Hz), 1.23 (m, 1H), 1.37 (m, 1H), 1.55–1.61 (m, 4H), 1.64–1.80 (m, 2H), 1.92 (m, 1H), 2.00 (m, 2H), 2.06 (d, 1H, $J = 14.4$ Hz), 2.23 (d, 1H, $J = 14.4$ Hz), 2.63 (br d, 1H, $J = 18.0$ Hz), 2.69 (dd, 1H, $J = 4.6$, 18.3 Hz), 4.35 (br d, 1H, $J = 4.4$ Hz), 5.15 (dd, 1H, $J = 9.0$, 15.2 Hz), 5.38 (dt, 1H, $J = 6.3$, 15.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 8.5, 11.7, 13.9, 25.5, 30.1, 30.2, 32.8, 37.6, 40.5, 43.4, 44.6, 80.8, 87.7, 97.9, 131.8, 134.2, 175.7.
11. $[\alpha]_D^{20}$ +56.6 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, 3H, $J = 7.4$ Hz), 1.50–1.62 (m, 1H), 1.64 (d, 3H, $J = 5.9$ Hz), 1.67–1.78 (m, 1H), 2.23–2.29 (m, 1H), 2.36–2.40 (m, 1H), 2.66 (dd, 1H, $J = 9.9$, 13.3 Hz), 3.28 (dd, 1H, $J = 3.2$, 13.3 Hz), 3.77–3.85 (m, 1H), 4.12–4.20 (m, 2H), 4.70 (br dddd, 1H, $J = 3.2$, 6.7, 6.9 Hz), 5.41–5.58 (m,

2H), 7.22–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 17.9, 24.5, 35.3, 38.0, 44.3, 55.4, 65.8, 127.3, 127.6, 127.8, 128.9, 129.4, 135.5, 153.2, 176.2.

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13. $[\alpha]_D^{20}$ −9.0 (*c* 0.03, $CHCl_3$), lit. $[\alpha]_D^{25}$ −10 (*c* 0.001, $CHCl_3$);[1b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (t, 3H, $J = 7.4$ Hz), 0.85 (t, 3H, $J = 7.4$ Hz), 0.97 (t, 3H, $J = 7.4$ Hz), 1.00 (t, 3H, $J = 7.4$ Hz), 1.15–1.26 (m, 1H), 1.35–1.44 (m, 1H), 1.45 (dd, 1H, $J = 9.2$, 14.3 Hz), 1.51–1.65 (m, 3H), 1.70 (dq, 1H, $J = 7.4$, 15.0 Hz), 1.76 (dq, 1H, $J = 7.4$, 15.0 Hz), 1.87–1.94 (m, 1H), 1.97 (d, 1H, $J = 14.5$ Hz), 1.98–2.05 (m, 2H), 2.18 (d, 1H, $J = 14.5$ Hz), 2.63 (d, 1H, $J = 18.2$ Hz), 2.70 (dd, 1H, $J = 4.8$, 18.2 Hz), 4.32 (d, 1H, $J = 4.3$ Hz), 5.10 (dd, 1H, $J = 9.2$, 15.3 Hz), 5.38 (dt, 1H, $J = 6.4$, 15.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3, 8.6, 11.6, 13.9, 25.5, 29.7, 30.2, 31.7, 37.5, 40.8, 43.5, 46.0, 80.0, 87.7, 98.0, 131.9, 133.9, 175.6.
14. $[\alpha]_D^{20}$ −245.9 (*c* 0.37, $CHCl_3$) authentic sample[15] $[\alpha]_D^{20}$ −226.9 (*c* 0.93, $CHCl_3$) and lit. $[\alpha]_D$ −175 (*c* 1.4, CCl_4).
15. The sample was provided by Professor Abimael D. Rodríguez, University of Puerto Rico; Jiménez, M. d. S.; Garzón, S. P.; Rodríguez, A. D. *J. Nat. Prod.* **2003**, *66*, 655–661.