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The first total synthesis and absolute stereochemistry of plakortone G from the Jamaican sponge *Plakortis* sp.

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Abstract—Total synthesis of plakortone G (**1**), a secondary metabolite of the Jamaican sponge *Plakortis* sp., was successfully achieved. The absolute configuration of this molecule was determined by comparison of the synthetic diastereomers with reported data to possess the (4*R*,8*R*)-configuration **14**.

From among the secondary metabolites of marine origin, the plakortone-family[1] consists of a synthetically attractive polyketide-framework carrying peroxide and tetrahydrofuranyl functionalities (Fig. 1).[2]

In addition, plakortones A–D, isolated from the Carribean sponge *Plakortis halichondrioides*, possessed an activating factor of cardiac SR-Ca^{2+}-pumping ATPase, which promotes relaxation of cardiac muscle. Accordingly, they may be a lead of chemotherapeutic agents for heart diseases. Plakortone G (**1**), isolated from the Jamaican sponge *Plakortis* sp., was reported to exhibit highly cytotoxic activity. The same carbon sequence of **1** as that of plakortide F, indicates that plakortide F would be a biosynthetic precursor of **1**.[1e] Since most plakortones have an activity of facile calcium entry into the sarcoplasmic reticulum, **1** might have the same activity; however, this point is still unclear. The relative and absolute configurations of **1** have not been revealed, along with those of other plakortones except plakortone

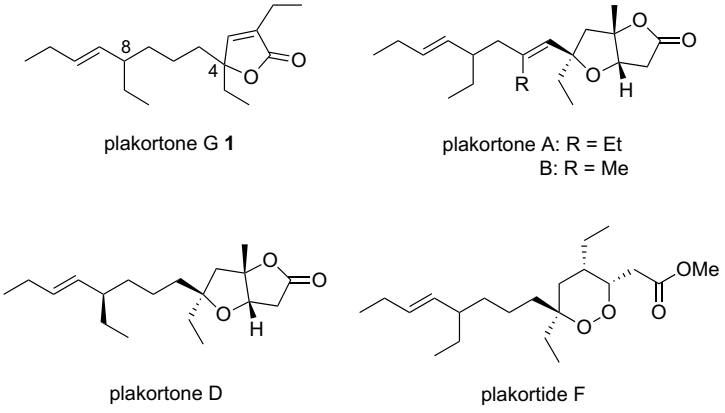

Figure 1. Structures of marine natural products from the marine sponge *Plakortis* sp.

Keywords: *Plakortis* sp.; α,β-Unsaturated γ-lactone; Absolute stereochemistry; Plakortones.
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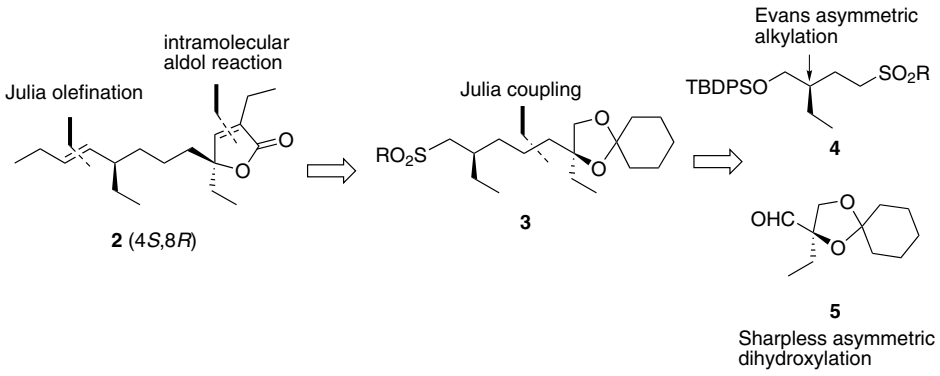
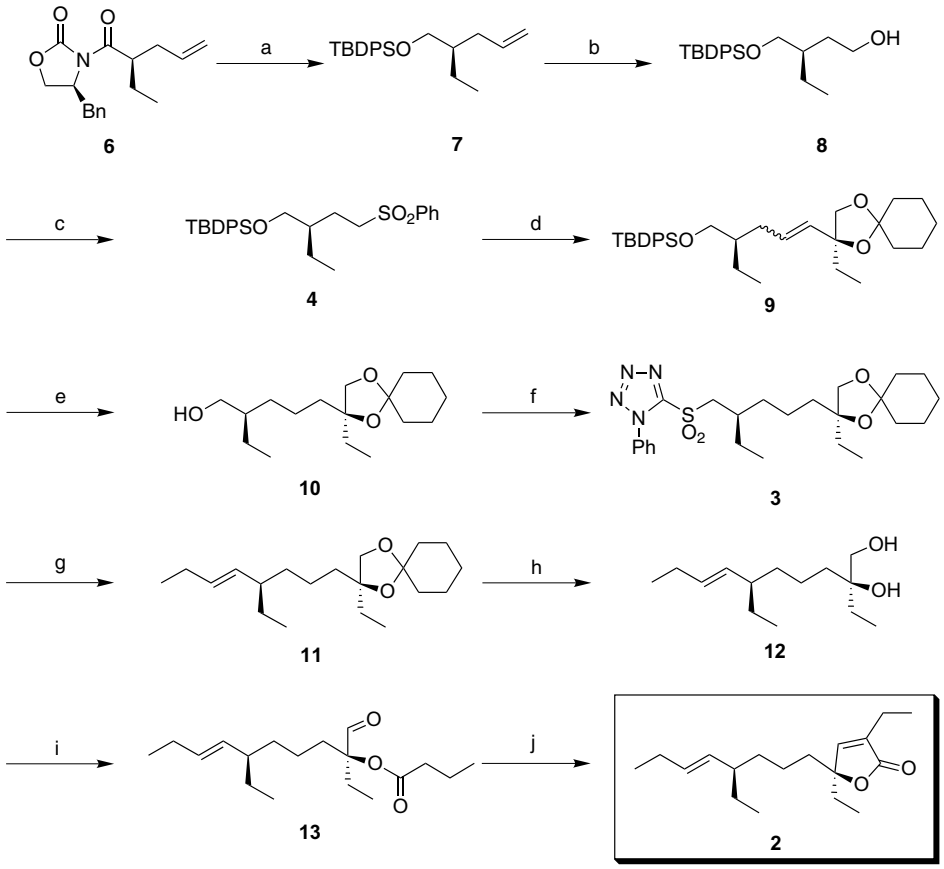
D, which was synthesized in an optically active form.[2g] We describe herein findings obtained in the synthesis of optically active **1**.

Plakortone G (**1**) possesses two asymmetric centers at the C-4 and C-8 positions. In addition to construction of the diastereomers, comparison of their spectral data and optical rotations with those of natural **1** would be required for determination of the absolute stereochemistry of **1**. The first target was **2** carrying the same (4*S*,8*R*)-configuration as that of plakortone D. Retrosynthetic analysis of **2** was elaborated as follows; the approach to **2** was based on an intramolecular aldol reaction to construct the α,β-unsaturated γ-lactone moiety, and the Julia olefination for selective *E*-olefination of **3**. Introduction of the asymmetric points at the C-4 and C-8 would be performed before construction of **3** by the Julia coupling reaction between the sulfone unit **4** and



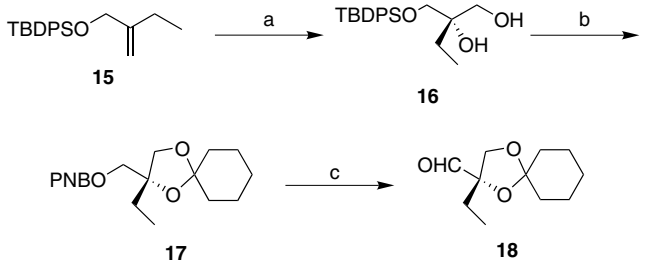
Scheme 1. Retrosynthetic analysis of compound (4*S*,8*R*)-**2**.



Scheme 2. Reagents and conditions: (a) i. $LiBH_4$, ii. TBDPSCl, imidazole, MS4A (73% in two steps); (b) i. OsO_4, NMO, $NaIO_4$ (94%), ii. $NaBH_4$ (100%); (c) i. PhSSPh, *n*-Bu_3P (97%), ii. *m*CPBA (100%); (d) i. *n*-BuLi, **5** (72%), ii. Ac_2O, Py, DMAP (97%), iii. 5% Na–Hg, Na_2HPO_4 (96%); (e) i. H_2, $Pd(OH)_2$–C (91%), ii. TBAF (95%), (f) i. TsCl, Et_3N, ii. 1-phenyl-1*H*-tetrazole-5-thiol, *t*-BuOK, iii. $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2 (73% in three steps); (g) LHMDS, propanal, DME (74%, *E*:*Z*, 3:2); (h) 2 M HCl (81%); (i) i. $SO_3\cdot$Py, DMSO, Et_3N (85%), ii. butyryl chloride, DMAP (79%); (j) i. LHMDS, ii. MsCl, Et_3N (85% in two steps).

the aldehyde unit **5**. Fragment **4** containing the asymmetric center at C-8 would be synthesized by the Evans asymmetric alkylation, and **5** containing the asymmetric center at the C-4 atom would be approached by the Sharpless asymmetric dihydroxylation (Scheme 1).

Synthesis of sulfone **4** commenced with the acyloxazolidinone derivative **6**, which was prepared by the Evans asymmetric alkylation with excellent stereoselectivity (94%, >99% de).[3] After reductive removal of the chiral auxiliary, protection of the primary alcohol by a TBDPS group gave **7**, which was subjected to oxidative cleavage by the Lemieux–Johnson oxidation, and reduction with $NaBH_4$. Substitution of the resulting alcohol **8**, followed by oxidation with *m*CPBA, gave sulfone **4** in good yield. According to the Hale protocol,[4] aldehyde **5** was synthesized by the Sharpless asymmetric dihydroxylation.[5] In the next stage, the Julia coupling reaction was performed between **4** and **5** with *n*-BuLi, followed by acylation and reductive elimination to give alkene **9** (70% in three steps) as a geometrical mixture. Hydrogenation of alkene **9**, followed by deprotection of the TBDPS group produced alcohol **10**. After tosylation, substitution reaction with a thiolate anion generated from 1-phenyl-1*H*-tetrazole-5-thiol, followed by oxidation afforded **3** as the precursor of the one-pot Julia olefination.[6] The modified Julia olefination of **3** with propanal led to alkene **11** as a mixture of *E* and *Z* isomers (3:2). This *E*/*Z* mixture could only be separated by



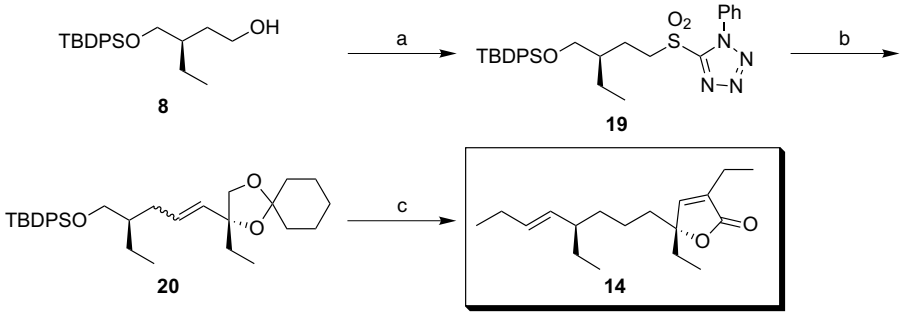
Scheme 3. Reagents and conditions: (a) AD-mix-α (93%); (b) i. cyclohexanone dimethylacetal, CSA (99%), ii. TBAF (100%), iii. PNBCl, Py, iv. recrystallization (38% in two steps); (c) i. K_2CO_3, MeOH (56%), ii. SO_3·Py, DMSO, Et_3N (64%).

$AgNO_3$-coated PTLC. Acid hydrolysis of the acetal group in (*E*)-**11** gave diol **12** in 81% yield. Oxidation of the primary alcohol in **12**, and successive acylation afforded **13**, a precursor of the intramolecular aldol reaction. Compound **13** was cyclized with LHMDS, followed by dehydration with MsCl to give the α,β-unsaturated γ-lactone **2**[7] (Scheme 2).

Comparison of the ^1H NMR data of synthetic **2** with the reported data indicated an obvious difference at the C-5 methylene proton {natural product: δ 1.61 ppm (isolated signal), **2**: δ 1.67–1.85 ppm (overlapping with other signals)}. This result indicated that natural plakortone G (**1**) has a different relative stereochemistry from that of **2**. Accordingly, we undertook synthesis of **14** carrying the (4*R*,8*R*)-configuration in the next stage. The vicinal diol **16** was synthesized by the asymmetric dihydroxylation from alkene **15**. In spite of the low enantiomeric excess of this AD reaction (78% ee), recrystallization of the *p*-nitrobenzoate derivative **17**, followed by hydrolysis and oxidation gave aldehyde **18** as a pure enantiomer (>99% ee) (Scheme 3).

Sulfone **19** was obtained by substitution reaction of **8** by a similar procedure to the case of **4**. The modified Julia coupling reaction of **19** with **18** gave alkene **20** in 85% yield. Compound **20** was derivatized by essentially the same procedure as in the case of **2** to afford (4*R*,8*R*)-**14**,[8] the ^1H NMR data and ^{13}C NMR data of which were superimposable to those reported. In addition, the optical rotation of **14** was identical with the natural data {syn. $[\alpha]_D^{20}$ −25.3 (*c* 0.0083, $CHCl_3$), nat.[1e] $[\alpha]_D$ −25.91 (*c* 0.0083, $CHCl_3$)}. Accordingly, the stereochemistry of plakortone G (**1**) should be determined as **14** (Scheme 4).

In conclusion, the first total synthesis and determination of the relative and absolute stereochemistry of plakortone G (**1**) to possess the (4*R*,8*R*)-configuration **14** were accomplished by comparison of the spectral data and optical rotation of the synthetic samples with those of the natural product. These results will contribute toward the synthesis of more complicated congeners carrying the same carbon-framework and the creation of biologically more potent substances.



Scheme 4. Reagents and conditions: (a) i. 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, *n*-Bu_3P (75%), ii. $(NH_4)_6Mo_7O_{24}$·$4H_2O$, H_2O_2 (100%); (b) LHMDS, **18** (85%); (c) i. H_2, $Pd(OH)_2$–C (92%), ii. TBAF (quant.), iii. TsCl, Et_3N, iv. 1-phenyl-1*H*-tetrazole-5-thiol, *t*-BuOK (88%), v. $(NH_4)_6Mo_7O_{24}$·$4H_2O$, H_2O_2 (97%), vi. LHMDS, propanal, DME (77%, *E*:*Z*, 3:2), vii. 2M HCl (82%), viii. SO_3·Py, DMSO, Et_3N (64%), ix. butyryl chloride, DMAP (63%), x. LHMDS, xi. MsCl, Et_3N (40% in two steps).

Acknowledgements

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7. **2**: $[\alpha]_D^{26}$ +31.3 (*c* 0.0083, $CHCl_3$); IR (film) *v* 1757, 1460, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, t, $J = 7.3$ Hz), 0.82 (3H, t, $J = 7.3$ Hz), 0.96 (3H, t, $J = 7.3$ Hz), 1.15 (3H, t, $J = 7.3$ Hz), 1.18 (2H, m), 1.26–1.36 (4H, complex), 1.67–1.75 (3H, complex), 1.79 (2H, complex), 2.00 (2H, complex), 2.30 (2H, dq, $J = 7.3$, 1.5 Hz), 5.03 (1H, dd, $J = 15.1$, 8.8 Hz), 5.36 (1H, dt, $J = 15.1$, 6.4 Hz), 6.82 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 12.2, 12.6, 14.8, 19.1, 21.7, 26.2, 28.7, 30.6, 35.6, 37.3, 44.7, 89.8, 132.8, 133.4, 136.3, 150.5, 173.9. HRMS (EI) calcd for $C_{18}H_{30}O_2$ (M^+) 278.2244, found: *m*/*z* 278.2246.
8. **14**: $[\alpha]_D^{20}$ −25.3 (*c* 0.0083, $CHCl_3$); IR (film) *v* 1755, 1460, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3H, t, $J = 7.3$ Hz), 0.82 (3H, t, $J = 7.3$ Hz), 0.96 (3H, t, $J = 7.3$ Hz), 1.15 (3H, t, $J = 7.3$ Hz), 1.16 (4H, complex), 1.25 (1H, m), 1.32 (1H, m), 1.60 (1H, m), 1.68–1.85 (4H, complex), 1.99 (2H, complex), 2.29 (2H, dq, $J = 7.3$, 1.5 Hz), 5.02 (1H, dd, $J = 15.1$, 8.8 Hz), 5.35 (1H, dt, $J = 15.1$, 6.4 Hz), 6.83 (1H, t, $J = 1.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.4, 12.2, 12.6, 14.8, 19.1, 21.8, 26.2, 28.8, 30.5, 35.6, 37.4, 44.9, 89.8, 132.8, 133.4, 136.2, 150.6, 173.9. HRMS (EI) calcd for $C_{18}H_{30}O_2$ (M^+) 278.2244, found: *m*/*z* 278.2234.