Prostaglandins and Congeners. 19.[1] Vinylstannanes: Useful Organometallic Reagents for the Synthesis of Prostaglandins and Prostaglandin Intermediates

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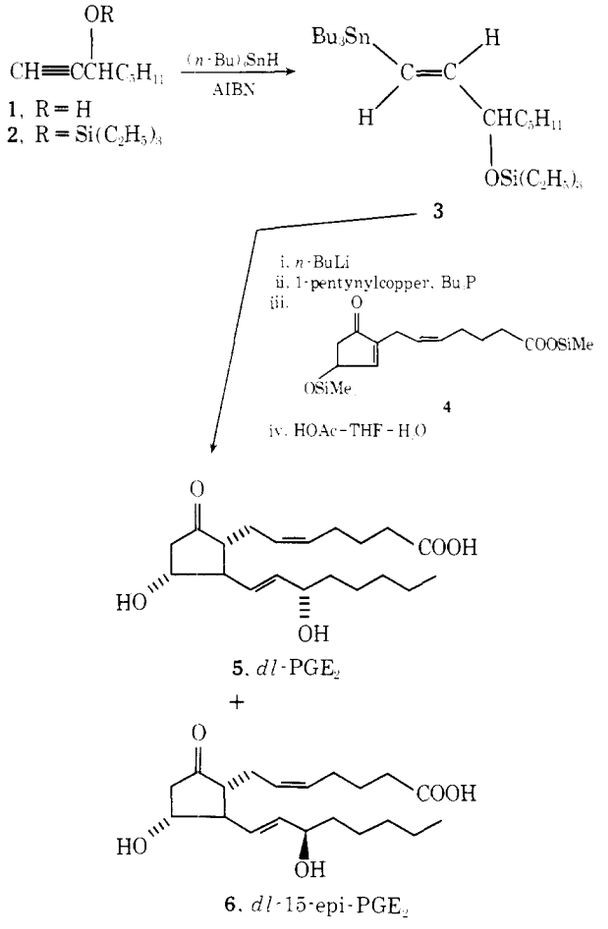
dl-PGE_2 and certain 15-deoxy-16-hydroxyprostaglandins were prepared by the conjugate addition to cyclopentenones of the mixed cuprate derived from the appropriately functionalized 1-alkenylstannanes. The preparation, *E*/*Z* ratio, and isomerization of (*E*)- and (*Z*)-1-(tri-*n*-butylstannyl)-1-alkenes from the corresponding 1-alkynes are discussed. In addition, the usefulness of (*E*)-1-alkenylstannyl reagent in providing a facile preparation of the corresponding (*E*)-1-iodo- or (*E*)-1-bromo-1-alkene is described.

Recent reports from these laboratories[2] and elsewhere[3] have described useful procedures for the synthesis of prostaglandins based upon the conjugate addition to cyclopentenones of (*E*)-1-alkenyl ligands of lithiocuprate derived from (*E*)-1-iodo-1-alkenes. We now report our efforts in utilizing the facile vinylstannyl cleavage[4,5] of readily available vinylstannane derivatives to generate the appropriately functionalized (*E*)-1-lithio-1-alkenyl reagents necessary for prostaglandin synthesis.

Treatment of 1-octyn-3-ol (**1**) with chlorotriethylsilane and imidazole in DMF[6] provided the silyl ether **2**, which upon treatment[7] with tri-*n*-butylstannane (TBS-H) in the presence of azobis(isobutyronitrile) (AIBN) was converted to (*E*)-1-(tri-*n*-butylstannyl)-3-(triethylsilyloxy)-1-octene (**3**) in 87% yield after distillation (Scheme I). None of the corresponding *Z* isomer of vinylstannane **3** was detectable in the ^{13}C NMR spectrum. We find it noteworthy that in situations wherein a trityloxy group is present in the molecule, no addition of TBS-H to an acetylene is noted.

Scheme I



Lithiation of vinylstannane **3** with 1 equiv of *n*-BuLi at −50 °C for 1 h, followed by addition of 1-pentynylcopper solubilized in tri-*n*-butylphosphine[8] and treatment of the resulting asymmetric cuprate with the trimethylsilyloxy protected cyclopentenone **4**[9] provided, after deblocking and dry-column chromatography, a 42% yield of *dl*-PGE_2 (**5**) and *dl*-15-epi-PGE_2 (**6**) in a ratio of ca. 40:60.[10,11]

This facile preparation of vinylstannanes was also extended to the β-chain precursors for 15-deoxy-16-hydroxyprostaglandins[2d,12,13] as illustrated in Scheme II. Hydrostannation of 4-methyl-4-(trimethylsilyloxy)-1-octyne[14] (**7**) with 1 equiv of TBS-H yielded (90%) 1-(tri-*n*-butylstannyl)-4-methyl-4-(trimethylsilyloxy)-1-octene (**8**) as an *E*/*Z* (**8a**/**8b**) mixture in the ratio of 10:1. The presence of the *Z* isomer **8b** was clear from the ^{13}C NMR spectrum; the signals due to carbons 1, 2, 3, and 1′ had minor side peaks shifted ±0.5–1.5 ppm attributable to the *Z* isomer. We have observed very similar ^{13}C NMR patterns in other functionalized vinylstannanes, although no separation was observed by TLC or GLC.

Vinylstannane **8** was lithiated with 1 equiv of *n*-BuLi at −35 °C for 2 h and converted to the mixed cuprate, which was conjugatively added to the bis(trimethylsilyloxy)cyclopentenone **9**[15] in the manner described above to furnish all racemic 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 (**10**) and all racemic 13-*cis*-15-deoxy-16-hydroxy-16-methylprostaglandin E_1 (**11**) in an overall 60% yield. The ratio of **10**/**11** was 12:1, approximately reflecting the original *E*/*Z* ratio of starting vinylstannane (**8a**/**8b**). The less polar 13-*cis* congener **11** was identified by comparison of the ^{13}C NMR spectrum of **11** with the spectrum of authentic 13-*cis*-15-deoxy-16-hydroxy-16-methylprostaglandin E_2.[16] The two 16-epimers of both **10** and **11** were not separable by TLC and HPLC, although the ^{13}C NMR spectrum clearly indicated the presence of two epimers in each instance.

Lithium–tin exchange of vinylstannane **8** was a slower process than that for the allylic counterpart **3**; under the conditions adequate for lithiation of **3** (1 equiv of *n*-BuLi, −50 °C, 1 h), **8** was only partially lithiated. We now routinely accomplish the lithium–tin exchange with 1 equiv of *n*-BuLi at −35 °C for 2 h in THF. We wish to point out that at this temperature, vinyl–tin cleavage is extremely slow in ether.[17]

In an effort to prepare the β-chain precursor **13b** for the synthesis of a 16,16-dimethylprostaglandin, trimethylsilyloxyoctyne[18] **12** was treated with TBS-H and AIBN. The product obtained gave a complex ^1H NMR spectrum, which upon careful inspection implied a 3:2 mixture of (*Z*)- and

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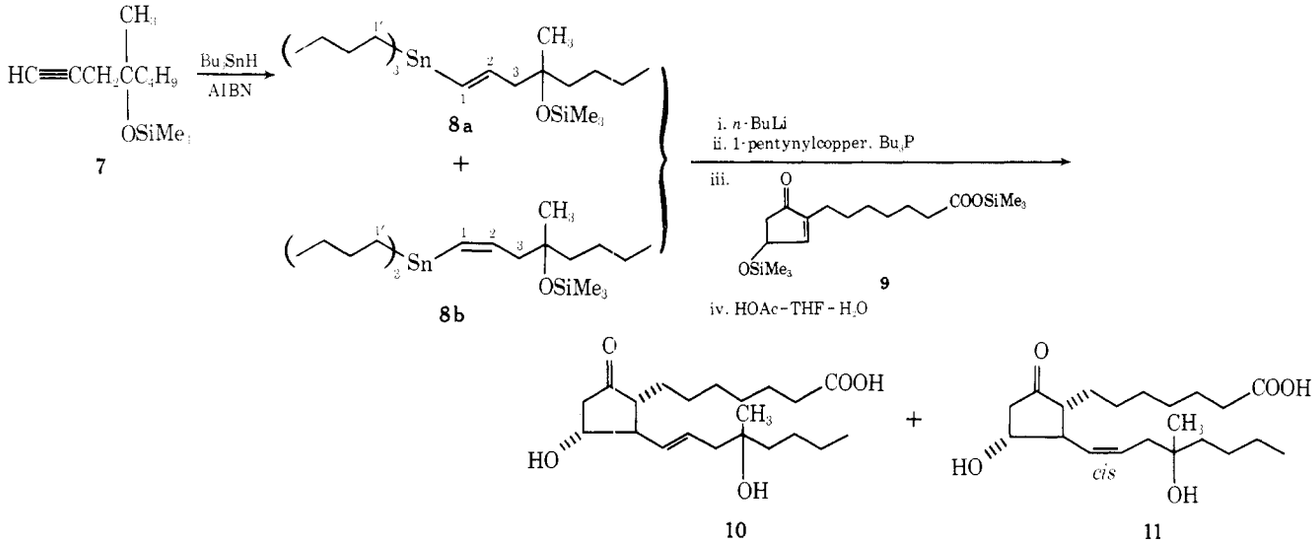
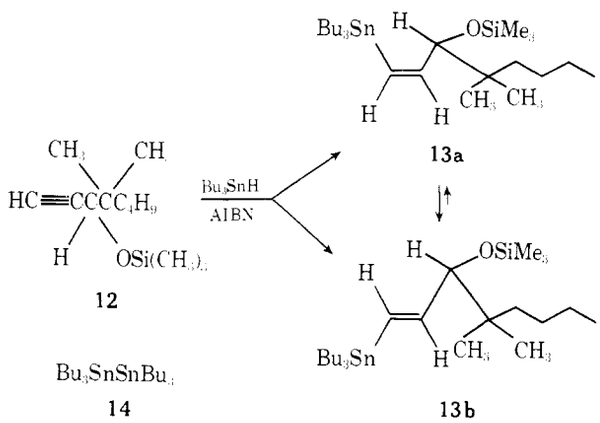
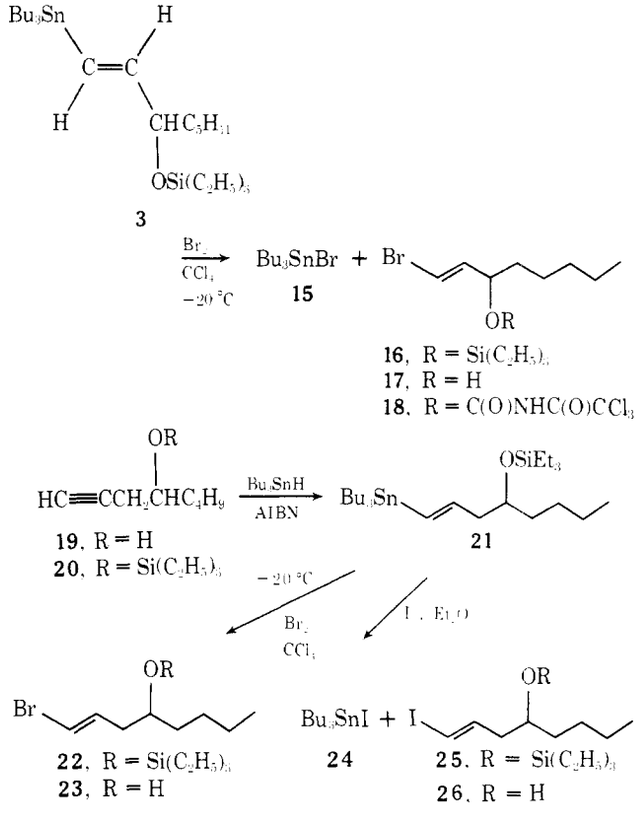
Scheme II



Scheme III



Scheme IV



(*E*)-vinylstannanes **13a** and **13b,** respectively (Scheme III). Lithiation of this mixture under the usual conditions (−50 °C, THF, 2 h) indicated that the *Z* isomer is considerably less reactive than the corresponding *E* isomer. Intrigued by this anomaly in the *E* vs. *Z* ratio, we investigated the conditions[19] necessary to isomerize **13a** to **13b.**

A sample of octyne **12** was treated with 0.9 equiv of TBS-H and a catalytic amount (0.2%) of AIBN (135 °C, 2 h). GLC (5% SE-30) and ^{1}H NMR spectrum indicated that the *Z* isomer **13a** was predominantly present (10:1 ratio). Further heating (2 h) produced no change on this ratio, nor did further heating after an additional 0.2 equiv of TBS-H was added; when fresh AIBN was added to the same reaction mixture, again no change was observed. However, when a second additional charge of TBS-H and AIBN was added to this reaction mixture, followed by heating, a *Z*/*E* ratio of 2:3 was observed. Further heating did not affect this ratio; but when a third charge of TBS-H and AIBN was added, a ratio of 1:9 (*Z*/*E*) was achieved.[20] A new peak appeared on GLC which had the identical retention time as hexa-*n*-butylditin (**14**). Apparently the destruction of excess TBS-H (bubbles were evident) becomes a competitive reaction when the rate of isomerization is decreased as in the case of the hindered 4,4-dimethyloctyne (**12**).

We have observed this unusual *Z*/*E* vinylstannane ratio with other propargylic ethers wherein there are substitutions adjacent to the silyloxy function. In such cases, we recommend the use of excess TBS-H in order to achieve a high *E*/*Z* ratio. It is apparent that the *E*/*Z* ratio cannot be assumed and must be determined in each instance.

Vinylstannanes represent useful precursors for various functionalized vinyl halides as illustrated in Scheme IV. When treated with 1 equiv of bromine in carbon tetrachloride[21] at −20 °C, the (*E*)-1-vinylstannane **3** was converted to bromotri-*n*-butylstannane (**15**) and (*E*)-1-vinyl bromide **16.** The stannane **15** can be easily removed by passing the reaction mixture through a short pad of silica gel with hexane. The triethylsilyl protecting group of the product **16** was unexpectedly cleaved to give **17,** which can then be reprotected. Inspection of the ^{1}H NMR spectrum of **17** did not enable us to characterize the double bond configuration. However, the exclusive trans nature of the vinyl bromide was confirmed from the ^{1}H NMR spectrum of the trichlorourethane derivative **18,** prepared in situ in a NMR tube with a few drops of trichloroacetyl isocyanate[22] ($J_{1,2}$ = 13.5 Hz), which was identical with the urethane prepared from an authentic

sample.[23] Vinyl bromide **17** has been used as a β-chain precursor for prostaglandin synthesis via Grignard conjugate addition.[23]

Similarly, vinylstannane **21**, prepared by treating 4-hydroxy-1-octyne[2d] (**19**) with chlorotriethylsilane to give **20** followed by addition of TBS-H and AIBN, was converted into the corresponding vinyl bromide **22** which, upon silica gel chromatography, provided the alcohol **23.**

Utilizing the stereospecific vinyl–tin cleavage reaction,[24] we have also investigated the transformation of vinylstannanes to the corresponding vinyl iodides,[3d] which undergo facile lithiation at −78 °C with *t*-BuLi and are used widely in prostaglandin synthesis.[2,3] Treatment of vinylstannane **21** with 1 equiv of iodine in ether furnished iodotri-*n*-butylstannane (**24**) and vinyl iodide **25.** The silyl protecting group of **25** was cleaved to provide **26** during purification (filtration with hexane through a short pad of silica gel to remove **24**).[25] Iodination of various functionalized vinylstannanes indicates that this transformation is both stereospecific and quantitative.[26]

Experimental Section

All reactions were performed under an atmosphere of argon or nitrogen. Solvents were removed under reduced pressure using a Büchi rotavapor followed by vacuum pumping. Boiling points are uncorrected. Dry-column chromatography was carried out with Woelm silica gel (equilibrated with 10% of the eluting solvent for several hours).

Infrared (IR) spectra were recorded with neat samples on a Perkin-Elmer Model 21 spectrophotometer or Nicolet 7199 FT-IR instrument. Proton magnetic resonance (^{1}H NMR) spectra were recorded in $CDCl_3$ solutions on HA-100D spectrometer. Carbon-13 magnetic resonance (^{13}C NMR) spectra were taken in $CDCl_3$ solutions on Varian XL-100FT NMR spectrometer (25.2 MHz). Chemical shifts of ^{1}H and ^{13}C NMR are given in parts per million downfield from an internal tetramethylsilane standard. Mass spectra (MS) were recorded on an AEI MS-9 instrument at 70 eV.

3-(Triethylsilyloxy)-1-octyne (2). To a stirred solution of 50 g (0.4 mol) of 1-octyn-3-ol and 83 g (1.22 mol) of imidazole in 500 mL of dry DMF, cooled in an ice bath to 5 °C under an atmosphere of nitrogen, was slowly added 90 g (0.6 mol) of triethylchlorosilane. After 15 min, the reaction mixture was warmed to room temperature and stirred overnight. It was then cautiously poured into a mixture of 500 g of ice and 750 mL of hexane with stirring. The aqueous phase was separated and extracted with hexane. The combined hexane extract was washed with water and brine and dried (anhydrous sodium sulfate). The solvent was removed under reduced pressure to give an oil which was vacuum distilled to afford 83.5 g (yield 87%) of colorless liquid: bp 70–72 °C (0.3 mm); ^{1}H NMR δ 2.35 (d, J = 2 Hz, C-1 H), 4.36 (td, J = 6 and 2 Hz, C-3 H); MS m/e 240 (M^+, calcd for $C_{14}H_{28}OSi$, 240.1904; found, 240.1901), 169 ($M - C_5H_{11}$).

(*E*)-1-(Tri-*n*-butylstannyl)-3-(triethylsilyloxy)-1-octene (3). To a stirred mixture of 20 g (78.6 mmol) of 3-(triethylsilyloxy)-1-octyne (**2**) and 150 mg of azobis(isobutyronitrile) was added 30 mL (113 mmol) of tri-*n*-butylstannane with a syringe under a nitrogen atmosphere. The mixture was heated at 130 °C and stirred for 2 h, then cooled to room temperature. The excess tri-*n*-butylstannane was removed by distillation at 70 °C (0.05 mm). The product was vacuum distilled at 165 °C (0.05 mm) to give 36.5 g (yield 87%) of colorless liquid: ^{1}H NMR δ 4.05 (br m, 1 H, C-3 H), 6.0 (m, 2 H, olefin); ^{13}C NMR δ 152.2 (C-2), 126.6 (C-1), 77.0 (C-3), 38.2 (C-4), 32.0, 29.3, 27.4, 25.1, 22.8, 14.1, 13.7, 9.6, 6.9, 5.1. Anal. Calcd for $C_{26}H_{56}OSiSn$: C, 58.76; H, 10.62. Found: C, 58.99; H, 10.69.

***dl*-Prostaglandin E_2 (5) and *dl*-15-Epiprostaglandin E_2 (6).** To a stirred solution of 3.2 g (6.0 mmol) of (*E*)-1-(tri-*n*-butylstannyl)-3-(triethylsilyloxy)-1-octene (**3**) in 2.5 mL of freshly distilled THF, cooled in a dry ice–acetone bath under an atmosphere of nitrogen, was added 2.6 mL (6.2 mmol) of *n*-BuLi (2.4 M in hexane) during 15 min. The resulting solution was stirred at the same temperature for 20 min, then at −50 °C for 1 h. To this resulting vinyllithium solution was added, at −78 °C, a solution of 0.79 g (7.02 mmol) of 1-pentynylcopper[27] and 2.43 g (12 mmol) of tri-*n*-butylphosphine in 4 mL of ether during 10 min. After stirring at −78 °C for 2 h, the mixed cuprate (yellow solution) was formed and a solution of 1.62 g (4.39 mmol) of 4-(trimethylsilyloxy)-2-(6′-carbotrimethylsilyloxy-2′-(*Z*)-hexenyl)cyclopent-2-en-1-one (**4**) in 3 mL of ether was added during 15 min. The mixture was allowed to stir at −78 °C for 10 min, then at −35 °C for 1.5 h, recooled to −70 °C and quenched by pouring into 100 mL of cold saturated NH_4Cl and 100 mL of ether. The aqueous layer was separated and extracted with ethyl acetate. The combined organic extract was washed with dilute HCl, water, and brine, and the solvent was evaporated to dryness to give a pale brown oil. The oil was treated with 30 mL of acetic acid, 15 mL of THF, and 7.5 mL of water and stirred at room temperature for 1 h, then diluted with toluene and concentrated in vacuo to dryness. The residual oil was applied to 15 g of silica gel (Silic ARCC-7) and washed with 80 mL of hexane followed by 100 mL of ethyl acetate; the ethyl acetate eluate was concentrated in vacuo to afford 2.4 g of yellow oil. This liquid was subjected to silica gel dry column chromatography, eluting with hexane–EtOAc–HOAc (20:80:1). From the column segments was isolated 395 mg of the less polar (R_f 0.5) *dl*-15-epi-PGE_2 (**6**): IR ν 3400 (OH), 1710 (C=O), 970 (*trans*-C=C); ^{1}H NMR δ 0.87 (br t, 20-CH_3), 2.75 (dd, J = 17 and 9 Hz, one of 10-CH_2), 4.06 (m, 11β-H and 15-H), 5.40 (m, Δ^5-H), 5.66 (m, Δ^{13}-H); ^{13}C NMR δ 214.8 (C-9), 177.7 (C-1), 136.6 (C-14), 130.8 (C-5), 130.1 (C-13), 126.9 (C-6), 72.4 (C-15), 72.1 (C-11), 54.9 (C-12), 51.1 (C-8), 46.4 (C-10), 37.1 (C-16), 33.2 (C-2), 31.8 (C-18), 26.4 (C-4), 25.2 (C-7), 25.0 (C-17), 24.6 (C-3), 22.6 (C-19), 14.0 (C-20); MS m/e 334 ($M - H_2O$, calcd for $C_{20}H_{30}O_4$, 334.2144; found, 334.2136), 316, 298, 190. The more polar (R_f 0.35) product (265 mg) was identified as *dl*-PGE_2 (**5**); IR ν 3400 (OH), 1710 (C=O), 970 (*trans*-C=C); ^{1}H NMR δ 0.87 (br t, 20-CH_3), 2.75 (dd, J = 17 and 7 Hz, one of 10-CH_2), 4.06 (m, 11β-H and 15-H), 5.36 (m, Δ^5-H), 5.60 (m, Δ^{13}-H); ^{13}C NMR δ 214.6 (C-9), 177.9 (C-1), 136.6 (C-14), 131.6 (C-13), 130.8 (C-5), 126.7 (C-6), 73.3 (C-15), 72.1 (C-11), 54.5 (C-12), 53.6 (C-8), 46.2 (C-10), 36.9 (C-16), 33.3 (C-2), 31.8 (C-18), 26.4 (C-4), 25.2 (C-7 and C-17), 24.5 (C-3), 22.6 (C-19), 14.0 (C-20); MS m/e 334 ($M - H_2O$, calcd for $C_{20}H_{30}O_4$, 334,2144; found, 334.2153), 316, 298, 190.

(*E*)-1-(Tri-*n*-butylstannyl)-4-methyl-4-(trimethylsilyloxy)-1-octene (8a). This material was prepared from the hydrostannation of **7** by the procedure described for the preparation of **3**: bp 150–155 °C (0.06 mm); IR ν 1600 (olefin); ^{1}H NMR δ 0.08 (s, Me_3Si), 1.20 (s, 4-CH_3), 2.30 (br s, 2H, C-3 H), 6.0 (m, 2 H, olefin); ^{13}C NMR (the numbers in parentheses denoted * indicate the chemical shifts due to the corresponding *Z* isomer **8b**) δ 146.1 (145.6*) (C-2), 130.5 (129.8*) (C-1), 76.0 (C-4), 51.2 (49.7*) (C-3), 42.2 (42.6*) (C-5), 29.2 (C-2′), 27.5 (4-CH_3), 27.3 (C-3′), 26.2 (C-6), 23.3 (C-7), 14.2 (C-8), 13.7 (C-4′), 9.52 (10.3*) (C-1′), 2.69 (Me_3Si). Anal. Calcd for $C_{24}H_{52}OSiSn$: C, 57.25; H, 10.41. Found: C, 57.12; H, 10.69.

All Racemic 15-Deoxy-16-hydroxy-16-methylprostaglandin E_1 (10) and All Racemic 13-*cis*-15-Deoxy-16-hydroxy-16-methylprostaglandin E_1 (11). To a stirred solution of 6.03 g (11.9 mmol) of (*E*)-1-(tri-*n*-butylstannyl)-4-methyl-4-(trimethylsilyloxy)-1-octene (**8a**) in 5 mL of THF, cooled in a dry ice–acetone bath under an atmosphere of nitrogen, was added 5.5 mL (12.0 mmol) of *n*-BuLi (2.2 M in hexane) during 15 min. The resulting solution was stirred at the same temperature for 10 min, then at −35 °C for 2 h. The following experiments (mixed cuprate formation, conjugate addition, deblocking, and dry-column chromatography) were performed in the manner described for the preparations of **5** and **6.** From the dry-column segments was isolated 2.1 g of all racemic 15-deoxy-16-hydroxy-16-methylprostaglandin E_1 (**10**) [^{1}H NMR δ 1.12 (s, 16-CH_3), 4.08 (q, J = 8 Hz, 11β-H), 5.45 (dd, J = 15 and 7 Hz, C-13 H), 5.72 (dt, J = 15 and 7 Hz, C-14 H); ^{13}C NMR[28] δ 215.5 (C-9), 133.8 (C-13), 129.5 (129.4) (C-14), 73.0 (72.9) (C-16), 71.9 (C-11), 54.6 (C-8 and C-12), 46.3 (C-10), 44.8 (C-17), 42.2 (41.1) C-15), 34.1 (C-2), 29.3, 28.8, 27.5, 26.4, 26.2, 26.1, 24.6, 23.3 (C-19), 14.1 (C-20); MS m/e 350 ($M - H_2O$, calcd for $C_{21}H_{34}O_4$, 350.2457; found, 350.2470), 335. 332, 317, 293, 275, 250, 232, 204] and 170 mg of all racemic 13-*cis*-15-deoxy-16-hydroxy-16-methyprostaglandin E_1 (**11**); ^{1}H NMR δ 1.46 (s, 16-CH_3), 4.00 (br q, J = 8 Hz, 11β-H), 5.48 (t, J = 9 Hz, C-13 H), 5.76 (m, C-14 H); ^{13}C NMR[28] δ 215.6 (C-9), 177.8 (C-1), 133,6 (C-13), 128.4 (128.2 (C-14), 73.3 (73.0) (C-16), 72.1 (C-11), 55.4 (C-8), 49.0 (C-12), 46.5 (C-10), 43.9 (40.4) (C-15), 39.2 (C-17), 34.2 (C-2), 29.3, 28.9, 27.1, 26.6, 26.0, 24.8, 24.5, 23.2 (C-19), 14.1 (C-20). MS m/e 350 ($M - H_2O$, calcd for $C_{21}H_{34}O_4$, 350.2457; found, 350.2477), 332, 275, 250, 232.

Preparation and Isomerization of (*Z*)- and (*E*)-1-(Tri-*n*-butylstannyl)-3-(trimethylsilyloxy)-4,4-dimethyl-1-octene (13a and 13b). A solution of 2 g (8.8 mmol) of 3-(trimethylsilyloxy)-4,4-dimethyl-1-octyne[18] (**12**), 2.6 mL (9.7 mmol, 1.1 equiv) of tri-*n*-butylstannane and 100 mg of azobis(isobutyronitrile) was stirred in an oil bath under an argon atmosphere and the temperature was raised gradually to 135 °C. After 2 h, an aliquot was analyzed by GLC (6 ft, 5% SE-30, oven temperature 230 °C), two peaks were observed at retention times of 4.7 and 5.1 min in a ratio of ~55:45, the former being assigned to (*E*)-1-(tri-*n*-butylstannyl)-3-(trimethylsilyloxy)-4,4-dimethyl-1-octene (**13b**) [^{1}H NMR δ 3.66 (m, C-3 H), 5.92 (m, olefin)] and the latter to the corresponding *Z* isomer **13a** [^{1}H NMR

δ 3.52 (d, J = 10 Hz, C-3 H), 5.91 (d, J = 14, C-1 H), 6.46 (dd, J = 14 and 10 Hz, C-2 H)].

This reaction mixture was distilled under vacuum to afford, after a forerun, the desired **13a/13b** product mixture; bp 140–142 °C (0.02 mm); MS m/e 457 (M − C_4H_9, calcd for $C_{21}H_{45}OSi^{116}Sn$, 457.2257; found, 457.2255), 367.

After three successive treatments of the above reaction mixture with additional TBS-H (0.6 mL each) and AIBN (10 mg each) at 135 °C for 2 h, the product E/Z ratio of approximately 9:1 was obtained. A peak of hexa-n-butylditin (Alfred Bader Co.) at a retention time of 7.2 min on GLC was also observed.

When the above experiment was repeated using 0.9 equiv (7.9 mmol) of tri-n-butylstannane, the initial product E/Z ratio (**13b/13a**) was 1:9 as evidenced by GLC and the ^{1}H NMR spectrum. After two successive treatments of the reaction mixture with additional TBS-H and AIBN as described above, this ratio was converted to 7:3.

(*E*)-1-Bromo-3-hydroxy-1-octene (17). To a stirred solution of 5.85 g (11.0 mmol) of (*E*)-1-(tri-n-butylstannyl)-3-(triethylsilyloxy)-1-octene (**3**) in 6 mL of CCl_4, cooled at −20 °C under an atmosphere of nitrogen, was added very slowly a solution of 1.759 g (11.0 mmol) of bromine in 6 mL of CCl_4 during a period of 1 h. After addition, the dropping funnel was rinsed with 0.5 mL of CCl_4 and the solution was added to the reaction mixture dropwise until a faint yellow color persisted. The solution was allowed to warm to room temperature and concentrated in vacuo to give a mixture of bromotri-n-butylstannane (**15**) and (*E*)-1-bromo-3-(triethylsilyloxy)-1-octene (**16**) as a colorless liquid; IR, no OH; ^{1}H NMR δ 4.10 (m, C-3 H), 6.21 (m, olefin). The liquid was applied to 60 g of silica gel (SilicAR CC-7) and washed with 300 mL of hexane followed by 300 mL of ethyl acetate. The hexane solution was concentrated in vacuo to give 4.6 g of bromotri-n-butylstannane (**15**); MS m/e 366 (M^+, calcd for $C_{12}H_{27}^{116}SnBr$, 366.0311; found, 366.0312), 309 (M − C_4H_9), 287. The ethyl acetate solution was concentrated in vacuo to give 3.1 g of (*E*)-1-bromo-3-hydroxy-1-octene (**17**): IR ν 3400 (OH), 1630 (C=C); ^{1}H NMR δ 4.10 (q, J = 6.5 Hz, C-3 H), 6.23 (dd, J = 13.5 and 6.5 Hz, C-2 H), 6.32 (d, J = 13.5 Hz, C-1 H); MS m/e 135 (M − C_5H_{11}, calcd for C_3H_4BrO, 134.9446; found, 134.9447), 127 (M − Br). A few drops of trichloroacetyl isocyanate was added to the ^{1}H NMR sample tube of **17** to provide the trichlorourethane derivative **18** and the ^{1}H NMR spectrum was recorded: δ 5.27 (q, J = 7.5 Hz, C-3 H), 6.19 (dd, J = 13.5 and 7.5 Hz, C-2 H), 6.55 (d, J = 13.5 Hz, C-1 H), 8.54 (br s, NH).

4-(Triethylsilyloxy)-1-octyne (20). This material was prepared from the silylation of **19** by the procedure described for the preparation of **2**: bp 54–54.5 °C (0.2 mm); ^{1}H NMR 1.97 (t, J = 3 Hz, C-1 H), 2.35 (dd, J = 6 and 3 Hz, C-3 H), 3.87 (br quintet, J = 6 Hz, C-4 H). Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 69.42; H, 11.89.

(*E*)-1-(Tri-*n*-butylstannyl)-4-(triethylsilyloxy)-1-octene (21). This material was prepared from the hydrostannation of **20** according to the procedure described for the preparation of **3**: ^{1}H NMR δ 2.30 (m, C-3 H), 3.68 (m, C-4 H), 5.92 (m, olefin); ^{13}C NMR δ 146.2 (C-2), 130.2 (C-1), 72.4 (C-4), 46.4 (C-3), 36.9 (C-5), 29.3, 27.7, 27.4, 23.0, 14.1, 13.7, 9.5, 7.0, 5.3.

Anal. Calcd for $C_{26}H_{56}OSiSn$: C, 58.75; H, 10.62. Found: C, 58.68; H, 11.06.

(*E*)-1-Bromo-4-hydroxy-1-octene (23). This material was prepared from **21** according to the procedure described for the preparation of **17**: IR ν 3400 (OH), 1630 (C=C); ^{1}H NMR δ 2.2 (t, J = 6 Hz, C-3 H), 3.66 (quintet, J = 6 Hz, C-4 H), 6.20 (m, 2 H, olefin); MS m/e 149 (151) (M − C_4H_9), 119 (212) (M − $C_5H_{11}O$).

(*E*)-1-Iodo-4-hydroxy-1-octene (26). To a stirred solution of 1.063 g (2 mmol) of (*E*)-1-(tri-n-butylstannyl)-4-(triethylsilyloxy)-1-octene (**21**) in 15 mL of ether was added 507 mg (2 mmol) of iodine portionwise. The solution was allowed to stir at room temperature for 2 h and a pale reddish color persisted in the reaction mixture. The solvent was evaporated in vacuo to dryness to give a mixture of iodotri-n-butylstannane (**24**) and (*E*)-1-iodo-4-(triethylsilyloxy)-1-octene (**25**) as a yellow liquid: IR ν 1605 (C=C), no OH; ^{1}H NMR δ 2.18 (t, J, 7 Hz, C-3 H), 3.68 (quintet, J = 7 Hz, C-4 H), 6.0 (d, J = 15 Hz, C-1 H), 6.52 (dt, J = 15 and 7.5 Hz, C-2 H); MS m/e 339 (M − C_2H_5), 311 (M − C_4H_9), 201 (M − C_3H_4I), 167 (C_3H_4I). This mixture was applied to 20 g of silica gel (SilicAR CC-4) and washed with 200 mL of hexane followed by 200 mL of ether. The hexane solution was concentrated in vacuo to give 0.75 g of iodotri-n-butylstannane (**24**). Anal. Calcd for $C_{12}H_{27}ISn$: C, 34.58; H 6.52. Found: C, 35.22; H, 6.62. The ether solution was concentrated in vacuo to give 0.57 g of (*E*)-1-iodo-4-hydroxy-5-octene (**26**); IR ν 3400 (OH), 1630 (C=C); ^{1}H NMR δ 2.14 (m, C-3 H), 3.64 (m, C-4 H), 6.10 (d, J = 15 Hz, C-1 H), 6.56 (dt, J = 15 and 7.5 Hz, C-2 H); MS m/e 254 (M^+, calcd for $C_8H_{15}IO$, 254.0169; found, 254.0171), 197 (M − C_4H_9), 167 (M − $C_5H_{11}O$).

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Registry No.—**1**, 37911-28-7; **2**, 66792-26-5; **3**, 66792-27-6; **4**, 59013-08-0; **5**, 22230-04-2; **6**, 31660-13-6; **7**, 66792-28-7; **8a**, 66792-29-8; **8b**, 66792-30-1; **9**, 63178-00-7; **10**, 66792-31-2; **11**, 66792-32-3; **12**, 64270-00-4; **13a**, 66792-33-4; **13b**, 66792-34-5; **15**, 1461-23-0; **16**, 66792-35-6; **17**, 52418-90-3; **18**, 66792-36-7; **19**, 52517-92-7; **20**, 66792-37-8; (*E*)-**21**, 66792-38-9; (*Z*)**21**, 66792-39-0; **22**, 66792-40-3; **23**, 66792-41-4; **24**, 7342-47-4; (*E*)-**25**, 66792-42-5; (*Z*)-**25**, 66792-43-6; (*E*)-**26**, 65989-29-9; (*Z*)-**26**, 66792-44-7; TBS-H, 688-73-3; triethylchlorosilane, 994-30-9.

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(1) For paper 18 in this series, see ref 9.
(2) (a) J. S. Skotnicki, R. E. Schaub, M. J. Weiss, and F. Dessy, *J. Med. Chem.*, **20**, 1042 (1977); (b) W. A. Hallett, A. Wissner, C. V. Grudzinskas, and M. J. Weiss, *Chem. Lett.*, 51 (1977); (c) W. A. Hallett et al., *Prostaglandins*, **13**, 409 (1977); (d) M. B. Floyd, R. E. Schaub, and M. J. Weiss, *ibid.*, **10**, 289 (1975).
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(5) (a) D. Seyferth, and L. G. Vaughan, *J. Am. Chem. Soc.*, **86**, 883 (1964); (b) D. Seyferth, and M. A. Weiner, *ibid.*, **83**, 3583 (1961).
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(9) M. B. Floyd, *J. Org. Chem.*, in press.
(10) The structures of *dl*-PGE_2 (**5**) and *dl*-15-epi-PGE_2 (**6**) were characterized on the basis of their chromatographic behaviors and spectral data and by comparison with *l*-PGE_2. The ^{1}H NMR and IR spectra of **5** and **6** are very similar (see Experimental Section).
(11) C. J. Sih and co-workers also noted in the conjugate addition preparation of prostaglandin E_1 that an excess of the 15-epi isomer was consistently obtained over the 15-normal isomer: C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti. *J. Am. Chem. Soc.*, **97**, 857 (1975); see also K. F. Bernady, J. F. Poletto, and M. J. Weiss, *Tetrahedron Lett.*, 765 (1975).
(12) M. Bruhn, C. H. Brown, P. W. Collins, J. R. Palmer, E. Z. Dajani, and R. Pappo, *Tetrahedron Lett.*, 235 (1976).
(13) P. W. Collins, E. Z. Dajani, M. S. Bruhn, C. H. Brown, J. R. Palmer, and R. Pappo, *Tetrahedron Lett.*, 4217 (1975).
(14) Compound **7** was prepared as follows: Grignard reaction of propargyl bromide with 2-hexanone to give 4-methyl-4-hydroxy-1-octyne, which was protected with trimethylchlorosilane and imidazole in DMF to furnish **7**: S-M. L. Chen and C. V. Grudzinskas, manuscript in preparation.
(15) Compound **9** was prepared from the unprotected cyclopentenone [G. Piancatelli and A. Scettri, *Tetrahedron Lett.*, 1131 (1977), and references cited therein] using hexamethyldisilazane–trimethylchlorosilane in pyridine; see also ref 9.
(16) S-M. L. Chen and C. V. Grudzinskas, manuscript in preparation.
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(25) The ^{13}C NMR spectrum of vinylstannane **21** indicated the presence of 20% of the corresponding *Z* isomer. Accordingly, the product vinyl iodide **25**

and **26** obtained were contaminated with 20% of the corresponding (*Z*)-1-vinyl iodide as evidenced by the ^1H and ^{13}C NMR spectra.

(26) A vinyl iodide incorporating the triethylsilyloxy functionality such as **25** has been utilized successfully in the synthesis of prostaglandin congeners in this laboratory.

(27) C. E. Castro, E. J. Gaughan, and D. C. Owlsey, *J. Org. Chem.*, **31**, 4071 (1966).

(28) The numbers in the parentheses represent the chemical shifts of the corresponding 16-epimer. The two peaks of those carbons are approximately of equal height.

Plakortin, an Antibiotic from *Plakortis halichondrioides*

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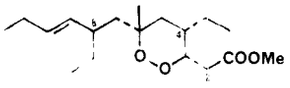
The Caribbean sponge *Plakortis halichondrioides* contains a lipid-soluble antibiotic, plakortin. The structure of plakortin (1) was deduced from spectroscopic data and by chemical degradation. Plakortin (1) was shown to be a cyclic peroxide. A related ketone (**12**) was isolated and the structure deduced from spectroscopic data.

Although there have been several large compilations of data recording in the in vitro antimicrobial activity of marine sponges,[2] relatively few of the metabolites responsible for antimicrobial activity have been isolated and identified.[3] Antimicrobial screening of crude extracts of some Caribbean sponges revealed that the crude ethanol extract of *Plakortis halichondrioides* (Wilson) inhibited the growth of *Staphylococcus aureus* and *Escherichia coli*. The antimicrobial activity was associated with the major metabolite of the sponge, which was named plakortin. In this paper, we wish to describe the structural elucidation of plakortin (1).



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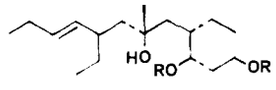


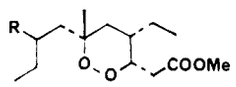
2 R = H
3 R = Ac

Plakortis halichondrioides (Wilson) was collected using SCUBA (−10 m) at Hookers Reef, Panama. The ether-soluble portion of an ethanol extract of the sponge was chromatographed on Florisil to obtain plakortin (1) (5.7% dry weight). Plakortin (1) had the molecular formula $C_{18}H_{32}O_4$. The infrared spectrum of plakortin (1) indicated the presence of an ester group (1735 cm^{-1}) and the absence of other carbonyl or hydroxyl groups. The ^{13}C NMR spectrum contained a carbonyl signal at δ 171.9 (s), a methoxyl signal at 51.5 (q), two signals for carbon atoms bearing oxygen at 81.0 (s) and 78.8 (d), and two signals at 134.4 (d) and 131.5 (d) due to a disubstituted olefin. The ^1H NMR spectrum confirmed the presence of a trans-disubstituted olefin [δ 5.38 (dt, 1 H, J = 15, 6, 6 Hz) and 5.10 (dd, 1 H, J = 15, 9 Hz)] and a methyl ester [δ 3.70 (s, 3 H)]. We therefore concluded that plakortin (1) was the methyl ester of a carboxylic acid containing a cyclic peroxide and a trans-disubstituted olefin.

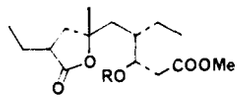
The ^1H spectrum also contained four additional methyl signals at δ 1.37 (s, 3 H), 0.97 (t, 3 H, J = 7 Hz), 0.90 (t, 3 H, J = 7 Hz), and 0.80 (t, 3 H, J = 7 Hz) and a signal assigned to the proton at C-3 at 4.49 (m, 1 H, J = 9.5, 6, 3.5 Hz) which was coupled to two mutually coupled signals at 3.05 (dd, 1 H, J = 15.5, 9.5 Hz) and 2.35 (dd, 1 H, J = 15.5, 3.5 Hz) and a third signal at 2.18 (m, 1 H). Since each of the triplet methyl signals must be adjacent to a methylene group, the structure of plakortin (1) could be solved by determining the position of the olefinic bond in the chain, its relationship to the peroxide ring, and the size of the peroxide ring.

The presence of the peroxide ring was confirmed by reduction of plakortin (1) with lithium aluminum hydride in dry ether at 0 °C to obtain the triol **2**. On acetylation with acetic anhydride in pyridine, the triol gave a diacetate **3**. By comparison of the ^1H NMR spectra of the triol **2** and the diacetate **3**, we deduced that the triol contained a primary alcohol, derived from reduction of the methyl ester, together with secondary and tertiary alcohols resulting from reduction of the cyclic peroxide ring.

Ozonolysis of plakortin (1), followed by addition of dimethyl sulfide to the ozonide, gave a mixture of an acid **5** and an aldehyde **4** which rapidly autoxidized to the acid **5**. The acid **5**, $C_{15}H_{26}O_6$, had lost a three-carbon fragment and contained only two methyl triplets at δ 0.97 and 0.92 in the ^1H NMR spectrum. Esterification of the acid **5** with diazomethane, followed by hydrogenation of the corresponding diester **6** over 10% palladium on charcoal, resulted in the formation on the γ-lactone **7** (IR 1765 cm^{-1}). The secondary alcohol function-

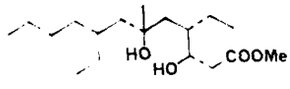


4 R = CHO
5 R = COOH
6 R = COOMe

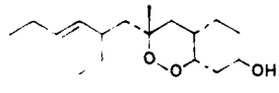


7 R = H
8 R = Ac

ality of the lactone **7** was acetylated with acetic anhydride in pyridine to obtain the corresponding acetate **8**. Hydrogenation of plakortin (1) under identical conditions resulted in the formation of a dihydroxy ester (**9**) which did not cyclize to a lactone, indicating that the ester which had resulted from cleavage of the olefin was involved in γ-lactone formation with the oxygen on the fully substituted carbon atom. Since the olefinic proton at δ 5.10 in plakortin (1) was coupled to only one nonolefinic proton, there must be an alkyl group at C-8.



9



10

Reduction of plakortin (1) with lithium tri-*tert*-butoxyaluminum hydride in refluxing ether resulted in reduction of the ester group, but not the peroxide bond, to obtain a primary alcohol **10**. The mutually coupled signals at δ 2.35 and 3.05 in the ^1H NMR spectrum of plakortin (1) were absent from the ^1H NMR spectrum of the alcohol **10**, suggesting that these signals were due to a methylene group situated between the

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