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SYNTHESIS OF ANTISECRETORY PROSTAGLANDINS USING VINYL TIN PRECURSORS

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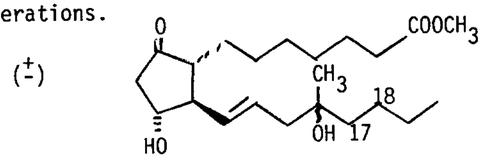
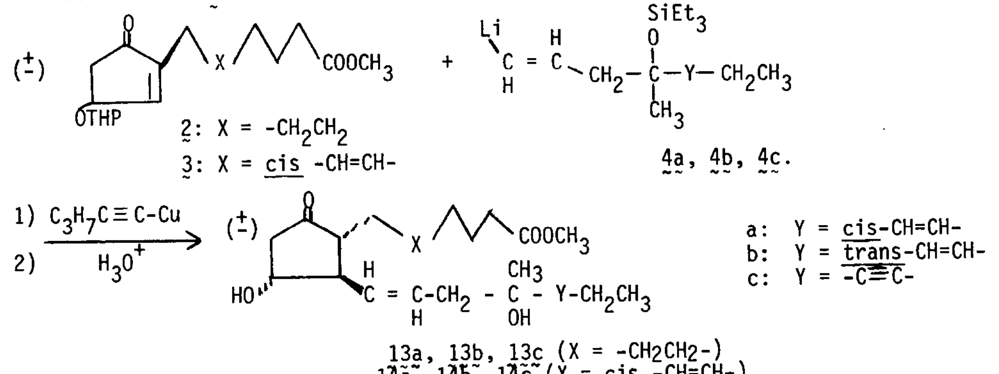
In an effort to expand our knowledge of the structure activity relationships in a series of 15-deoxy-16-hydroxy prostaglandins[1], we undertook the synthesis of analogs of 1 having a center of unsaturation at carbons 17 and 18. While the $\Delta^{17,18}$ cis analogs (13a, 14a) are of considerable interest because of their relationship to PGE_3, it was also desirable to prepare the trans (13b, 14b) and acetylenic (13c, 14c) compounds because of both pharmacological and synthetic considerations.



1

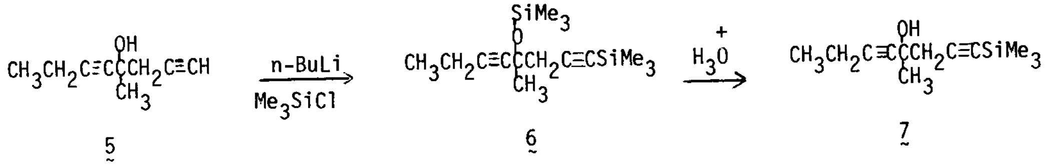
The conjugate addition reaction involving cuprate reagents was employed to obtain these compounds (Scheme I) and has been described previously[1]. The major obstacle in this synthesis was the preparation and conversion of the acetylenes 5, 9, and 10 to the corresponding vinyl lithium derivatives 4.

Scheme I



13a, 13b, 13c (X = -CH2CH2-)
14a, 14b, 14c (X = cis -CH=CH-)

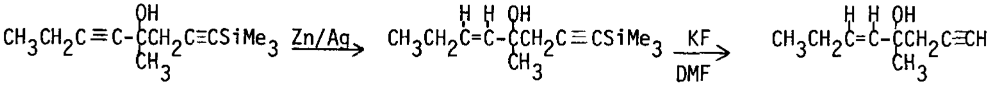
The starting diyne 5 was prepared by addition of the Grignard reagent derived from propargyl bromide to 3-hexyn-2-one[2]. Selective reduction of the internal triple bond of 5 was accomplished by utilizing the directing influence of the free hydroxy of 5[3], and also by protecting the terminal triple bond with a trimethylsilyl group. Thus 5 was first treated with two equivalents of n-butyl lithium at -60° followed by addition of two equivalents of tri-



$$\underset{5}{CH_3CH_2C{\equiv}C\overset{OH}{\underset{CH_3}{C}}CH_2C{\equiv}CH} \xrightarrow[Me_3SiCl]{n\text{-}BuLi} \underset{6}{CH_3CH_2C{\equiv}C\overset{\overset{SiMe_3}{O}}{\underset{CH_3}{C}}CH_2C{\equiv}CSiMe_3} \xrightarrow{H_3O^+} \underset{7}{CH_3CH_2C{\equiv}C\overset{OH}{\underset{CH_3}{C}}CH_2C{\equiv}CSiMe_3}$$

methylchlorosilane to give 6, which on hydrolysis with acetic acid, water, and tetrahydrofuran at room temperature yielded the free hydroxy compound 7.

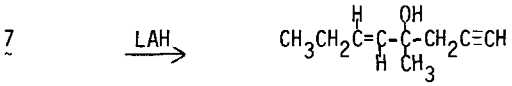
Reduction of 7 to the corresponding cis compound 8 (J = 12Hz) was accomplished by use of a zinc-silver couple (prepared from zinc, silver acetate and acetic acid)[3]. In this reaction the presence of the 1-silyl group of 7 is required because, in its absence, reduction of the terminal acetylene group to the olefin occurs. The terminal silyl moiety was removed from 8 by treatment with potassium fluoride in dimethylformamide to give 9.[4]



$$CH_3CH_2C\equiv C-\overset{OH}{\underset{CH_3}{C}}CH_2C\equiv CSiMe_3 \xrightarrow{Zn/Ag} CH_3CH_2\overset{H}{C}=\overset{H}{C}-\overset{OH}{\underset{CH_3}{C}}CH_2C\equiv CSiMe_3 \xrightarrow[DMF]{KF} CH_3CH_2\overset{H}{C}=\overset{H}{C}-\overset{OH}{\underset{CH_3}{C}}CH_2C\equiv CH$$

7 8 9

Reduction of 7 to the trans compound 10 (J = 15Hz) was carried out with lithium aluminum hydride. Interestingly, concomitant removal of the terminal trimethylsilyl group was observed in this reaction. The hydroxy acetylenes 5, 9 and 10 were converted to their respective triethylsilyl ethers with triethylchlorosilane and imidazole in dimethylformamide.[5]



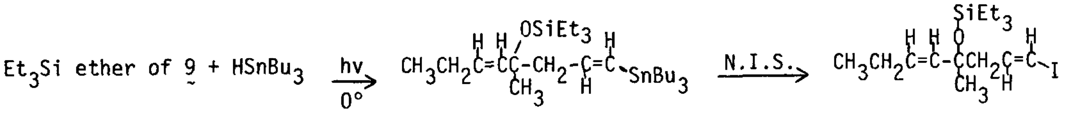
$$7 \xrightarrow{LAH} CH_3CH_2\overset{H}{C}=\underset{H}{C}-\overset{OH}{\underset{CH_3}{C}}-CH_2C\equiv CH$$

10

Difficulties were encountered when we attempted to convert these acetylenes to the corresponding trans-vinyl iodides using the conventional reagents catechol borane[6] or diisobutylaluminum hydride[7] followed by treatment with iodine. With both reagents, lack of selectivity of reaction with the unsaturated centers of the triethylsilyl ethers of 5, 9 and 10 gave a complex mixture of products[8].

We then investigated the use of tributyltin hydride as a method for conversion of acetylenes to trans-vinyl tin adducts which can be converted directly to vinyl lithium reagents[10] or to vinyl halides[11]. The literature procedure[10] utilized elevated temperatures and azobisisobutyronitrile as catalyst for this reaction. Under these conditions a mixture of products was obtained with the silyl ethers of 5, 9 and 10. In an attempt to find more selective reaction conditions, we investigated the use of ultraviolet irradiation as a means to promote this reaction. We found that hydrostannation is rapid (1 - 4 hours) and smooth at 0° when induced by light from an ordinary sunlamp, even when carried out in pyrex glassware[12]. In a typical experiment, the triethylsilyl ether of 9 (1 eq) and tributyltin hydride (1.1 eq) were placed in a pyrex flask without solvent and immersed in an icebath. The mixture was stirred under argon and irradiated for about 3 hours with a 275W GE Sunlamp placed about 10-12 cm from the flask. The course of the reaction was followed by thin layer chromatography on silica gel using hexane as eluent.

The resulting trans-vinylstannane 11 was dissolved in tetrahydrofuran, cooled to -20°



$$Et_3Si\ ether\ of\ 9 + HSnBu_3 \xrightarrow[0°]{h\nu} CH_3CH_2\overset{H}{C}=\overset{H}{C}-\overset{OSiEt_3}{\underset{CH_3}{C}}-CH_2-\underset{H}{C}=\overset{H}{C}-SnBu_3 \xrightarrow{N.I.S.} CH_3CH_2\overset{H}{C}=\overset{H}{C}-\overset{\overset{SiEt_3}{O}}{\underset{CH_3}{C}}CH_2\underset{H}{C}=\overset{H}{C}-I$$

11 12

and treated dropwise with a tetrahydrofuran solution of N-iodosuccinimide[11,13] to give after vacuum distillation the *trans*-vinyl iodide **12** [b.p. 100-120° (0.05 mm); PMR($CDCl_3$): δ6.59 C_2,m;δ5.98 C_1[d(14.7)]; δ5.16-5.42,C_{5-6} m(12)]. Conversion of **12** in the usual manner[1] to the cuprate reagent and subsequent reaction with **2** and **3** gave **13a** and **14a** respectively (Scheme I). Likewise **5** and **10** were utilized to prepare **13b**, **13c**, **14b** and **14c**. All of these compounds were potent gastric antisecretory agents in the dog[1].

In their work on the hydrostannation of homopropargylic alcohols, Corey and coworkers reported obtaining a *trans* to *cis* ratio of 85:15 which was not affected by temperature or steric factors[14]. Also, Seyferth and Vaughan[15] found that ultraviolet irradiation of simple alkenyltrialkylstannanes resulted in a steady state mixture of 75% *trans* and 25% *cis*. In view of these facts, we carefully investigated our system for the presence of *cis* products using 4-methyl-4-trimethylsilyloxy-1-octyne (**15**) as a model. Equal molar amounts of **15** and tributyltin hydride were mixed and irradiated at 0° with a sunlamp. Samples were withdrawn at 1 hour and 7 hour intervals. The remainder was irradiated at 50-55° for 16 additional hours. Analysis by ^{13}C NMR[16] established the *trans/cis* ratios of the samples: 1 hour: 64/36; 7 hours: 84/16; 23 hours: 84/16.[17] Thus the steady state *trans/cis* ratio for this system is 84/16 which is consistent with Corey's data[14]. In the presently described prostaglandin syntheses carried out via the iodides, 10-15% of $\Delta^{13,14}$ *cis* prostaglandins were present and were easily separated from the corresponding *trans* compounds by chromatography[1]. However, in prostaglandin syntheses in which the direct lithiation of the vinylstannanes was utilized, the amounts of $\Delta^{13,14}$ *cis* prostaglandins observed varied from zero to 15%. In an attempt to explain this variability, the following experiment was conducted: a sample of the hydrostannation product of **15** having a *trans/cis* ratio of 3:1 was treated at -70° for one hour with one equivalent of n-butyl lithium and then was quenched with water. The unreacted vinylstannane[18] was separated from the reaction products by chromatography (silica gel, 100% hexane). Analysis by ^{13}C NMR revealed that the *trans/cis* ratio of the vinylstannane had changed to 2/3.

Thus the rate of exchange with n-butyl lithium of the cis-vinyl-stannane is appreciably less than that of the corresponding trans compound. The extent of the exchange of the cis-vinylstannane is therefore dependent on time and temperature, and variations in these reaction conditions affect the amount of $\Delta^{13,14}$ *cis prostaglandin eventually obtained. This observation could have far-reaching influence on the future use of trialkyltin hydride in organic synthesis.*

For example, this discovery allowed us in practice to virtually exclude (less than 5%) the formation of $\Delta^{13,14}$ *cis* compounds in the preparation of prostaglandins such as **1** using the following procedure: The tributyl tin hydride adduct of **15** (*trans/cis* ratio: 84/16) (2 mmol) was dissolved in 8 ml of dry THF, cooled to -70° under N_2 and treated with n-BuLi (1.7 mmol). The solution was stirred at -70° for 20 min., after which a solution of pentynylcopper (2 mmol) and hexamethylphosphorus triamide (4 mmol)[19] in 4 ml of ether was added. A solution of **2** (1 mmol) in 3 ml of ether was added after 10 min. The reaction mixture was stirred at -70° for 2 hours and then poured into a mixture of ether and 1N HCl. The ether layer was washed with H_2O, filtered, dried (Na_2SO_4) and stripped of solvent. Chromatography[1] followed by removal of protecting groups with acetic acid, H_2O and THF (3:1:1, 25° 18 hr) provided **1** (50% yield from **2**).

In view of Corey's findings[10] that propargylic alcohols yield almost exclusively the *trans* isomer upon hydrostannation, we decided to study the light induced hydrostannation of 3-methyl-3-trimethylsilyloxy-1-octyne (**16**) which is a precursor of another antisecretory prostaglandin[20]. Irradiation of equivalent amounts of **16** and tributyltin hydride at 0° for 1 hour produced an approximately 1:1 mixture of the *cis* (J = 14.5 Hz) and *trans* (δ6.01, s, 2H)[21] adducts which, surprisingly, were separable by thin layer and column chromatography (silica gel, 100% hexane). When irradiation was continued without cooling (50-55°) for 2 hours, complete isomerization of the *cis* to the *trans* compound occurred. Also remarkable was the finding that the *cis*-vinylstannane did not react to an appreciable extent with n-butyl lithium even at room temperature. In contrast, the corresponding *trans* compound reacted smoothly with n-butyl lithium at -60° to give the vinyl lithium derivative which was converted to racemic 15-methyl PGE$_1$ via the corresponding cuprate reagent. This example dramatizes the difference between the *cis* and *trans* vinylstannanes in their rate of exchange with butyl lithium.

Application of this hydrostannation technique to other systems is currently under investigation.

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17. When a 25% excess of tributyltin hydride was used the steady state ratio was reached after 1 hour at 0°.
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