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ORGANOPALLADIUM APPROACHES TO PROSTAGLANDINS. 9.[1] SYNTHESIS OF A PROSTAGLANDIN ENDOPEROXIDE ANALOGUE BY ALLYLPALLADATION-OZONOLYSIS OF NORBORNENE

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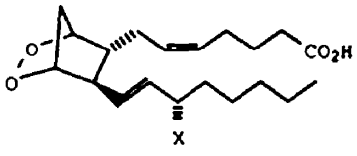
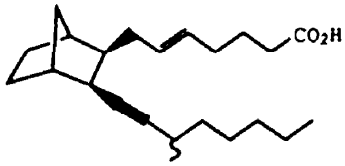
Abstract- Norbornene reacts with π-allylpalladium hexafluoroacetylacetonate (5), followed by triphenylphosphine and the optically active lithium acetylide of 3-tetrahydropyranyloxy-5-(-)-1-octyne to form the enyne 7. Selective ozonolysis, Wittig olefination and deprotection afford prostaglandin endoperoxide analogue 4.

The prostaglandin endoperoxides 1 (PGG_2) and 2 (PGH_2) are central to the biosynthesis of the primary prostaglandins, the leukotrienes, and the thromboxanes. The extraordinary



1 X = OOH (PGG_2)
2 X = OH (PGH_2)



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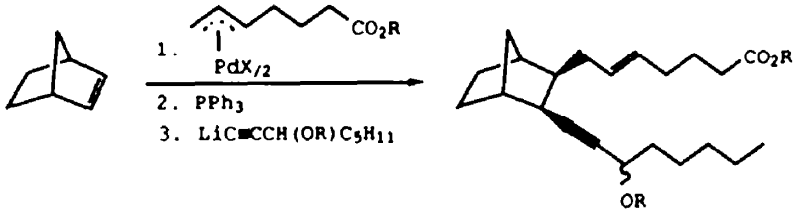
biological potency of PGG_2 and PGH_2 and their extreme instability have spurred interest in the synthesis of stable analogues.[2,3] While the most common routes to these compounds have involved either modification of naturally occurring prostaglandins or Diels-Alder approaches, we have developed benzylpalladation,[4,5] thienylpalladation,[6,7] oxypalladation,[8] carboethoxymethylpalladation,[9] vinylpalladation[10] and allylpalladation[11] approaches to a wide variety of novel new endoperoxide analogues. Of our new compounds, to date the most potent inhibitor of arachidonic acid-induced blood platelet aggregation has been analogue 3 (as a mixture of all possible epimers at C-15 and the points of side chain attachment) prepared by an allylpalladation approach (eq. 1).[11] We, therefore, sought for biological testing an



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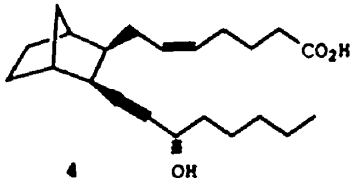
efficient route to isomer 4 which retains the *cis*-5,6-double bond present in the naturally



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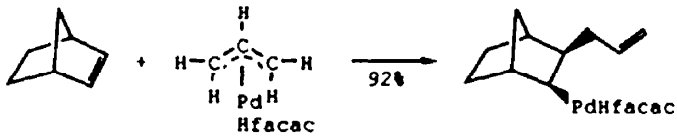
occurring prostaglandins. We are happy to report here the successful synthesis of compound 4 using a modification of our allylpalladation approach.

Results and Discussion

Since neither the traditional approaches to prostaglandin endoperoxide analogues, such as the Diels-Alder reaction or modifications of naturally occurring prostaglandins, nor any of our earlier organopalladium approaches were directly applicable to the preparation of compound 4, we have developed a modification of our earlier allylpalladation approach. Because π-allylpalladium compounds are known to add to bicyclic alkenes to afford exclusively the *trans* product, we sought an indirect way to introduce the desired *cis* double bond. An approach which introduces an acetaldehyde moiety onto the bicyclic skeleton was particularly appealing, since subsequent Wittig olefination of the aldehyde would introduce in one step the desired carboxylic acid side chain with the correct stereochemistry. Indeed, this approach has proven quite successful as outlined below.

The two side chains of the desired prostaglandin analogue were readily introduced by the reaction of norbornene with π-allylpalladium hexafluoroacetylacetonate (5), using a standard literature procedure[11,12] (eq. 2), followed by reaction with the optically active lithium



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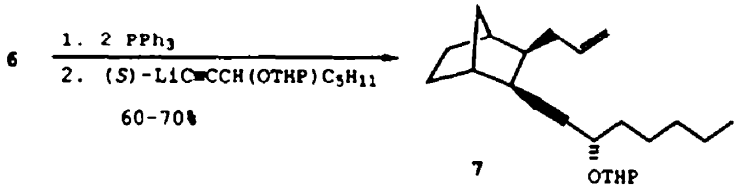
acetylide of 3-tetrahydropyranyloxy-S-(-)-1-octyne using our previously developed procedure[11] (eq. 3).



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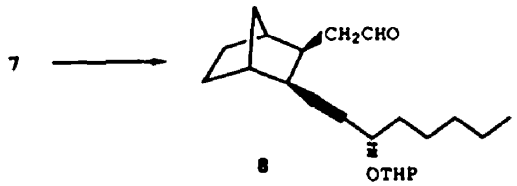
The success of this overall approach depended upon finding a selective method for oxidizing compound 7 to the desired aldehyde 8 (eq. 4). The use of catalytic amounts of



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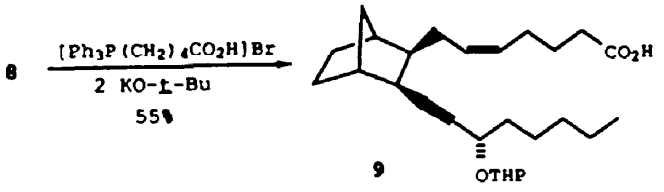
osmium tetroxide and excess sodium metaperiodate[13] under a variety of reaction conditions (1-4% OsO_4, 1.5 h-overnight, 100-200% $NaIO_4$) all resulted in mixtures of the desired aldehyde 8 and the corresponding carboxylic acid.

Since acetylenes are known to be slow to undergo ozonolysis[14] and selective ozonolysis of a carbon-carbon double bond in the presence of an acetylene has been accomplished,[15] we have examined this approach. Accordingly, ozonolysis of enyne 7 at -78°C was attempted in the presence of pyridine, since pyridine has been shown to moderate the reactivity of ozone[16] (eq.

4). Subsequent work-up using zinc and acetic acid gave the aldehyde 8 in 50% unoptimized yield.

The Wittig olefination of aldehyde 8 was best effected using KO-t-Bu and the appropriate phosphonium salt (eq. 5).[17] Hydrolysis with 4:2:1 acetic acid/THF/water[18] at 45°C for 9 h gave compound 4 in 90% yield.



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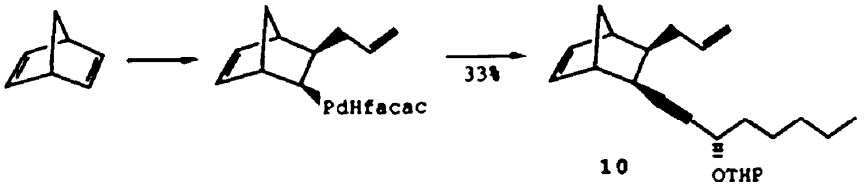
It should be noted that the product 4 of this sequence is inherently a pair of diastereomers resulting from addition of the two side chains to opposite ends of the original norbornene double bond, but the diastereomers could never be observed by ^1H NMR spectroscopy and they could not be separated at any stage of the overall sequence. ^{13}C NMR spectroscopic analysis of the product 4, however, does indicate the presence of two extra peaks in the aliphatic region. We assume that the diastereomers are there in approximately a 1:1 mixture.

Compound 4, as a pair of diastereomers, has been tested in human platelets using both an 800 μM arachidonic acid challenge and an ADP challenge. Some activity [I_{50}'s (μM) respectively of ~140 and ~500] against both stimulating agents has been observed suggesting non-selectivity, but the level of activity is on the lower fringe of significance so interpretation is hazardous.

Attempts to extend this overall reaction sequence to bicyclo[2.2.2]oct-2-ene and norbornadiene have been disappointing. While the organopalladium adducts of these two olefins corresponding to compound 6 can easily be prepared,[12] lithium acetylide displacement of the bicyclooctylpalladium compound afforded $PhC{\equiv}CCH(OTHP)C_5H_{11}$ as the major product and the yield of displacement product 10 from the norbornadiene adduct was only 33% (eq. 6). The latter



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compound 10 also failed to undergo selective ozonolysis bringing an end to our attempts to generalize this process.

Experimental Section

All chemicals were used as obtained commercially unless otherwise noted. The following chemicals were purchased from Aldrich Chemical Co.: triphenylphosphine, hexafluoroacetylacetone, norbornene, 1-octyn-3-ol, potassium t-butoxide and (4-carboxybutyl)-triphenylphosphonium bromide. Silver acetate was obtained from Fisher Scientific Co. Triphenylphosphine was recrystallized from ethanol before use. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride. π-Allylpalladium chloride was prepared according to the literature procedure.[19] S-(-)-1-Octyn-3-ol was kindly provided by Dr. Fumihiko Kondo.

3-Tetrahydropyranyloxy-S-(-)-1-octyne was prepared from the alcohol using a standard literature procedure.[20]

Synthesis of compound 6. π-Allylpalladium chloride dimer (0.910 g, 2.5 mmol) and purified silver acetate (0.880 g, 5.25 mmol) were added to chloroform (200 ml). The mixture was stirred at room temperature for 70 min and then filtered to remove the silver chloride precipitate. Hexafluoroacetylacetone (1.10 ml, 7.5 mmol) was added to the filtrate, which was stirred for 40 min, and the resultant solution was filtered through Celite and evaporated to dryness on a rotary evaporator. The yellow solid thus obtained was freed of acetic acid by placing it under a high vacuum for 1-2 h. The yield of compound 5 was 94%: ^{1}H NMR ($CDCl_3$) δ 3.13 (d, 2 H, J = 12 Hz, anti CH-C-CH), 4.20 (d, 2 H, J = 7 Hz, syn CH-C-CH), 5.70 (overlapping tt, 1 H, J = 12 Hz and J = 7 Hz, C-CH-C), 6.09 (s, 1 H, Hfacac).

Norbornene (0.480 g, 5.06 mmol) and compound 5 (1.63 g, 4.6 mmol) were dissolved in methylene chloride (21 ml). The solution was stirred at room temperature for 24 h and then chromatographed on a florisil column using methylene chloride as the eluant. Compound 6 was obtained as a yellow solid in 92% yield after removal of methylene chloride: ^{1}H NMR ($CDCl_3$) δ 1.0 - 2.60 (m, 11 H), 3.28 (dd, 1 H, J = 7 Hz and J = 2 Hz, PdCH), 4.28 (dd, 1 H, J = 14 Hz and J = 1 Hz, cis C-C=C-H), 4.39 (dd, 1 H, J = 8 Hz and J = 1 Hz, trans C-C=C-H), 5.79 (m, 1 H, C-CH=C), 5.97 (s, 1 H, Hfacac).

Synthesis of compound 7. Compound 6 (1.80 g, 4.0 mmol) was weighed into an oven-dried round bottom flask fitted with a septum and gas inlet tube. The system was flushed with nitrogen and 30 ml of freshly distilled benzene was added by syringe, followed by triphenylphosphine (2.10 g, 8.0 mmol). The mixture was stirred for 5 min and the benzene was evaporated on a rotary evaporator followed by a high vacuum pump. Tetrahydrofuran (34 ml) was added by syringe and the reaction mixture was then cooled to -78°C. The lithium acetylide solution, the preparation of which is outlined below, was added using a stainless steel transfer needle. The acetylide solution was prepared as follows. 3-Tetrahydropyranyloxy-S-(-)-1-octyne (0.880 g, 4.20 mmol) and 25 ml of tetrahydrofuran were added to an oven-dried round bottom flask fitted with a septum and gas inlet tube. The system was flushed with nitrogen and cooled to -78°C. n-Butyllithium (4.70 mmol) was added with stirring to the solution of the acetylene. The reaction was stirred at -78°C for 10 min, warmed to -25°C for 20 min, and then cooled again to -78°C prior to addition to the organopalladium compound. After addition, the combined reaction mixture was stirred at -78°C for 1 h, warmed to -25°C for 3 h, and then warmed to room temperature. The reaction mixture was stirred at room temperature for 36 h. Methanol (1 ml) was added to quench the reaction and the solvent was removed on a rotary evaporator. The resultant gummy, black residue was extracted with hexane (3 x 50 ml) and the combined extracts were filtered. After removal of the solvent, the extraction process was repeated twice more and the resultant orange oil was chromatographed on silica gel using 19:1 benzene/ethyl acetate as the eluant. Compound 7 was obtained in 60% yield: ^{1}H NMR ($CDCl_3$) δ 0.80-2.40 (m, 28 H), 2.48 (bd, 1 H, J = 8 Hz, HCC_2C), 3.29-4.78 (m, 4 H, CH_2O, C_3CCHO- and -OCHO-), 4.92 (d, 1 H, J = 9 Hz, trans C-C=C-H), 4.96 (d, 1 H, J = 17 Hz, cis C-C=C-H), 5.58-6.00 (m, 1 H, C-CH=C); IR (neat) 3060, 2950, 2870, 2220, 1640, 1465, 1070, 980, 910, 865, 670 cm^{-1}.

Synthesis of compound 8. A general published procedure for ozonolysis was employed.[16] A solution of compound 7 (0.791 g, 2.30 mmol) and freshly distilled pyridine (0.22 ml) in dry methylene chloride (23 ml) was cooled to -78°C. Ozone was bubbled through the solution at approximately 1 mmol/min. After approximately 1.6 equivalents of ozone were added, the reaction was stopped and the solution was added immediately to zinc dust (1.18 g) in a round bottom flask. Glacial acetic acid (2.36 ml) was also added and the flask was warmed to room temperature by means of a water bath. After the reaction mixture was stirred for 2 h, it was

filtered, diluted with hexane (25 ml) and washed three times with water. Crushed ice was added and washing was continued with 10 ml portions of 5% sodium hydroxide and then with water. Each washing was extracted with 1:1 methylene chloride/hexane. The combined extracts were dried over sodium sulfate and concentrated. Purification by column chromatography on silica gel using 4:1 hexane/ethyl acetate gave compound 8 (0.398 g) in 50% yield: ^{1}H NMR ($DCCl_3$) (300 MHz) δ 0.82-2.41 (m, 28 H), 2.56-2.66 (d, 1 H, J = 8 Hz, CH-C≡C-), 3.45-4.05 (m, 2 H, CH_2O), 4.20-4.41 (m, 1 H, C≡CCHO-), 4.69-4.94 (m, 1 H, -OCHO-), 9.74-9.84 (br s, 1 H, aldehyde); IR (neat) 2940, 2860, 2710, 2220, 1715, 1440, 1430, 1100, 1060, 1010, 970, 900, 710 cm^{-1}; ^{13}C NMR ($DCCl_3$) δ 14.05, 19.54, 22.63, 25.07, 25.29, 28.17, 29.70, 30.70, 31.61, 34.16, 36.14, 38.66, 39.64, 39.75, 41.60, 44.51, 44.66, 47.61, 62.34, 65.32, 82.67, 83.69, 86.93, 95.47, 98.00, 201.91; mass spectrum, m/e 290.1879 [calcd for $C_{19}H_{26}O_3$ (M^+-C_4H_8), 290.1882].

Synthesis of compound 9. A general published procedure for Wittig olefination was employed.[17] Potassium t-butoxide (0.550 g, 4.93 mmol) was slowly added with stirring to a dry THF solution (9 ml) of (4-carboxybutyl)triphenylphosphonium bromide (1.06 g, 2.46 mmol) under an atmosphere of nitrogen at room temperature. The deep red solution was then stirred for 15 min. To this was slowly added aldehyde 9 (0.210 g, 0.607 mmol) in dry THF (6 ml). The solution turned chocolate brown and was stirred for 3 h. Water (50 ml) and 2N H_2SO_4 (30 ml) were then added. Extraction with diethyl ether gave an organic fraction which was again washed with 2N H_2SO_4 (2 x 20 ml) and water (3 x 20 ml) and dried. Purification by column chromatography on silica gel using 1:1 hexane/ethyl acetate gave 160 mg (55%) of the title compound: ^{1}H NMR ($CDCl_3$) (300 MHz) δ 0.83-0.94 (poorly resolved m, 3 H), 1.03-2.67 (m, 32 H), 3.46-4.12 (m, 2 H), 4.72-5.10 (m, 1 H), 5.27-5.56 (m, 2 H); IR (neat) 3400-2400 (OH), 2940, 2860, 1710, 1450, 1020, 900, 730 cm^{-1}.

Synthesis of compound 4. Compound 9 was dissolved in 2.13 ml of acetic acid, 1.06 ml of THF and 0.53 ml of water (4:2:1) and heated at 45°C for 9 h.[18] The solvents were evaporated. The residue was taken up in ether and washed with water, dried over magnesium sulfate and concentrated. Column chromatography on silica gel using 1:1 hexane/ethyl acetate plus a few drops of acetic acid gave 115 mg of compound 4 (90%): ^{1}H NMR ($CDCl_3$) (300 MHz) δ 0.8-2.60 (m, 29 H), 4.10 (m, 1 H, C≡CCHO-), 5.25-5.60 (m, 2 H, CH=CH), 6.2-6.8 (b, 2 H, OH and COOH); ^{13}C NMR ($CDCl_3$) δ 14.03, 22.64, 24.37, 24.98, 26.35, 28.49, 29.92, 30.59, 31.55, 32.58, 33.78, 38.12, 38.20, 38.98, 39.99, 44.73, 44.79, 45.53, 63.03, 83.08, 86.97, 128.57, 131.40, 177.64; IR (neat) 3600-2400 (acid, OH), 2940, 2860, 2220, 1710, 900, 720 cm^{-1}; mass spectrum, m/e 346.25093 (calcd for $C_{22}H_{34}O_3$, 346.25080). Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.24; H, 9.90. Found: C, 76.47; H, 10.07. Compound 4 is inherently a pair of diastereomers, but they could not be separated by TLC, nor observed by ^{1}H NMR spectroscopy. However, ^{13}C NMR spectroscopy shows two extra peaks in the aliphatic region.

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