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ORGANOPALLADIUM APPROACHES TO PROSTAGLANDINS 1.

SYNTHESIS OF THIOPHENE-CONTAINING PROSTAGLANDIN ENDOPEROXIDE ANALOGS VIA THIENYLPALLADATION OF BICYCLIC OLEFINS

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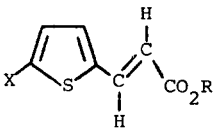
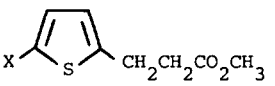
Summary Thiophene-containing prostaglandin endoperoxide analogs are readily available by addition of thienylpalladium species to bicyclic olefins and subsequent treatment with alkenyl or alkynyl organometallics. Hydrogenation affords bicyclic and tricyclic prostanoic acid analogs.

The discovery of the bicyclic endoperoxides PGG and PGH as highly biologically active intermediates in prostaglandin biosynthesis has prompted the synthesis of a number of analogs [1] The majority of approaches to date have utilized the Diels-Alder reaction or simply modified the naturally occurring primary prostaglandins. We became interested in the possibility of employing organopalladium chemistry in the construction of prostaglandin endoperoxide analogs and wish at this time to report the facile synthesis of a number of new, biologically active thiophene-containing endoperoxide analogs via thienylpalladation of bicyclic olefins.

trans-3-(2-Thienyl)acrylic acid, 1, is commercially available and readily esterified to the corresponding methyl ester, 2, in 88% yield. Hydrogenation[2] and acid catalyzed esterification of 1 provides the saturated methyl ester 3 (79% yield). Both esters are readily mercurated



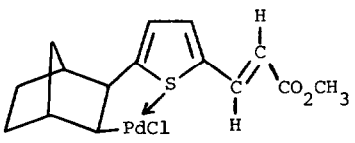
	X	R
1	H	H
2	H	CH_3
4	HgCl	CH_3



3 X = H
5 X = HgCl

(2 equiv $HgCl_2$, 10 equiv. NaOAc, aqueous ethanol) in the 5-position to afford the corresponding organomercurials 4 and 5 in yields of 86% and 83% respectively. Addition of these organomercurials to an acetonitrile solution of norbornene, palladium chloride and lithium chloride (10 1 >2) under nitrogen at 0°C and warming to room temperature afforded the bright yellow air stable adducts 6 [mp 165°C(dec), ^1H NMR ($CDCl_3$) δ 0.7-1 9 (6H, m), 2.45-3 30

(4H, m), 3.73 (3H, s), 6 00 (1H, d, J=16 Hz), 6.66 (1H, d, J=4 Hz), 6 97 (1H, d, J=4 Hz), 7 60 (1H, d, J=16 Hz), IR (max)(KBr) 1740 (C=O), 1170 (C-O)cm^{-1}. Anal. ($C_{15}H_{17}ClO_2PdS$) C, 44.68; H, 4 25, O, 7.96, S, 7 94 Found· C, 44.90, H, 4.37, O, 8.02, S, 8 03] and 7 [mp 155-157°C (dec), ^1H NMR ($CDCl_3$) δ 0 8-1.8 (6H, m), 2.35-3.2 (8H, m), 3.68 (3H, s), 6.62 (1H, d, J=3.5 Hz), 6.98 (1H, d, J=3 5 Hz), IR (max)(KBr) 1740 (C=O), 1170 (C-O)cm^{-1}. Anal. ($C_{15}H_{19}ClO_2PdS$) C, 44 46, H, 4.73; O, 7.90, S, 7.91. Found C, 44 65; H, 4 82, O, 8 15, S, 8.04] which precipitated from solution in 67% and 78% yields respectively. The



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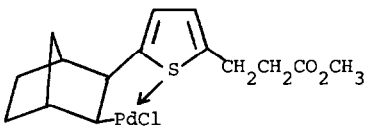

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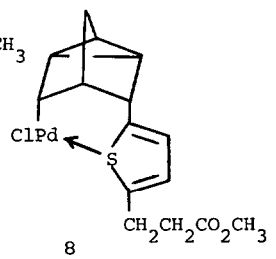

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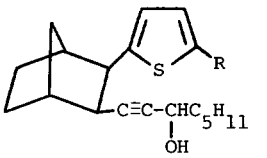
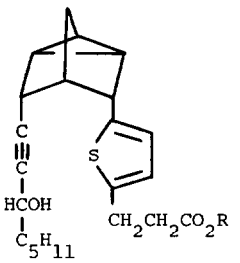
analogous reaction of 5 and norbornadiene provided the nortricyclyl adduct 8 [mp 181-182°C (dec); ^1H NMR ($CDCl_3$) δ 1.45 (2H, br s), 1.6-1.9 (2H, m), 1.9-2 1 (2H, m), 2.2-2.5 (2H, m), 2.5-3.2 (4H, m), 3.72 (3H, s), 6.73 (2H, s), IR (max)(KBr) 1730 (C=O)cm^{-1} Anal. ($C_{15}H_{17}ClO_2PdS$) C, 44.69, H, 4.25. Found C, 44.56, H, 4.53] in 74% yield.

The unsaturated alcohol side chain of the prostaglandins was most easily introduced by a three step procedure involving (1) conversion of the organopalladium chloride to the corresponding hexafluoroacetylacetonate (Hfacac)(AgOAc followed by the diketone), (2) addition of 2 equivalents of triphenylphosphine in tetrahydrofuran (THF), cooling to -78°C, addition of a -78°C THF solution of 1 equivalent of 1-lithio-3-(2-tetrahydropyranyloxy)-1-octyne followed by slow warming to room temperature overnight and work-up, and (3) removal of the THP protecting group (cat p-TsOH in methanol, 4-6 hr. at room temperature) This approach affords exclusively the exo isomers In this manner the novel thiophene-containing prostaglandin endoperoxide analogs 9a [64% overall yield, ^1H NMR ($CDCl_3$) δ 0.7-2 2 (16H, m), 2.45 (2H, br s), 2.75 (1H, dt, J=2 Hz, J=8 Hz), 3.12 (1H, d, J=8 Hz), 3 73 (3H, s), 4 00 (1H, br s), 6.00 (1H, d, J=16 Hz), 6.66 (1H, d, J=4 Hz), 6.97 (1H, d, J=4 Hz), 7 60 (1H, d, J=16 Hz); IR (max) ($CHCl_3$) 1710 (C=O), 1620 (C=C), 1160 (C-O)cm^{-1}, m/e 386.19013 (calcd for $C_{23}H_{30}O_3S$, 386.19157)], 10a [58% yield, ^1H NMR ($CDCl_3$) δ 0 7-2.2 (18H, m), 2 3-3 5 (8H, m), 3.68 (3H, s), 4.05 (1H, m), 6.55 (2H, s), IR (max) ($CHCl_3$) 1740 (C=O), 1175 (C-O)cm^{-1}, m/e 388.20905 (calcd for $C_{23}H_{32}O_3S$, 388.20722)] and 11a [62% yield, ^1H NMR ($CDCl_3$) δ 0.9-1 02 (3H, br t, J=4 Hz), 1.1-1.8 (17H, m), 2.25-2.80 (4H, m), 3 0-3.25 (3H, m), 3 70 (3H, s), 3.90 (1H, br s), 6.62 (1H, d, J=4 Hz), 6.73 (1H, dd, J=1 Hz, J=4 Hz), IR (max) ($CHCl_3$) 1730 (C=O),

m/e 386.19258 (calcd for $C_{23}H_{30}O_3S$, 386.19157)] were prepared. Saponification (refluxing 2N KOH, aqueous methanol, 1 hr.) afforded the corresponding carboxylic acids 9b [96% yield,



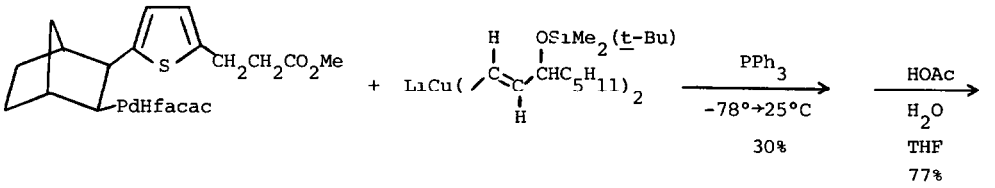
9a R = trans-CH=CHCO$_2$CH$_3$
9b R = trans-CH=CHCO$_2$H
10a R = CH$_2$CH$_2$CO$_2$CH$_3$
10b R = CH$_2$CH$_2$CO$_2$H

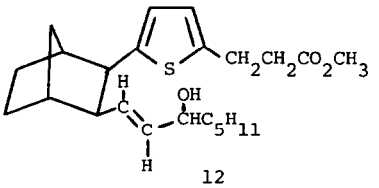


11a R = CH$_3$
11b R = H

^{1}H NMR ($CDCl_3$) δ 0.8-2.2 (18H, m), 2 3-2 66 (2H, br s), 2.8 (1H, d, J=9 Hz), 3 2 (1H, d, J=9 Hz), 4 08 (1H, m), 6.07 (1H, d, J=16 Hz), 6.6-7.2 (4H, m), 7.75 (1H, d, J=16 Hz), IR(max) ($CHCl_3$) 1670 (C=O), 1615 (C=C), 1205 (C-O)cm^{-1}; m/e 372.17707 (calcd for $C_{23}H_{28}O_3S$, 372 17970)], 10b [82% yield; ^{1}H NMR ($CDCl_3$) δ 0.7-2.2 (17H, m), 2.3-3.5 (8H, m), 4.10 (1H, m), 6 38 (2H, s), 6.60 (2H, s), IR (max)($CHCl_3$) 1720 (C=O)cm^{-1}, m/e 374.19307 (calcd for $C_{22}H_{30}O_3S$, 374.19157)] and 11b [86% yield, ^{1}H NMR ($CDCl_3$) δ 0.7-1.9 (20H, m), 2.2-2.9 (4H, m), 2 9-3 3 (3H, m), 3.90 (1H, m), 6 6 (2H, m), IR (max) ($CHCl_3$) 1715 (C=O)cm^{-1}, m/e 372.17825 (calcd for $C_{22}H_{28}O_3S$, 372.17970)]

Efforts have been made to directly introduce the trans-allylic alcohol side chain into these analogs. Best results to date have been obtained using organocopper reagents on the organopalladium hexafluoroacetylacetonate complexes [12 23% yield; ^{1}H NMR ($CDCl_3$) δ 0.8-2.2 (18H, m), 2.3-3.2 (8H, m), 3 67 (3H, s), 3 7-3 85 (1H, m), 5.1-5.3 (2H, m), 6.4-6.6 (2H, m), IR (max) ($CHCl_3$) 1730 (C=O), 960 (trans C=C)cm^{-1}, m/e 390.22283 (calcd for $C_{23}H_{34}O_3S$, 390.22288)]. Further work on this reaction is necessary however





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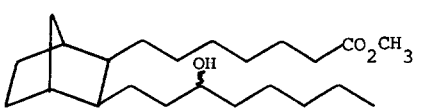
Incorporation of the thiophene ring into prostaglandin endoperoxide analogs has several very attractive features. First of all, a number of heterocyclic prostaglandin analogs have already shown substantial biological activity. Introduction of a phenyl unit in the acid side chain has also provided a number of compounds of biological interest.[3] The heterocyclic ring also forces the acid side chain to adopt a configuration analogous to the cis-5,6 olefinic side chain found in the naturally occurring prostaglandins Finally, the thiophene ring provides a site for further chemical elaboration. While we have so far failed in our attempts to reduce the thiophene ring to the corresponding 2,5-dihydrothiophene and eventually remove the sulfur to afford cis-5,6 substrates, hydrogenation with Raney Nickel of compounds 10a and 11a provides a simple approach to the interesting cyclic prostanoic acid derivatives 13 [82% yield, ^{1}H NMR ($CDCl_3$) δ 0.8-1.0 (3H, t, J=6 Hz), 1 1-1 9 (30H, m), 1.9-2 1 (3H, br s), 2 3 (2H, t, J=7 Hz), 3 7 (4H, s, overlapping peaks), IR (max) (neat) 3420 (OH), 1740 (C=O)cm^{-1}, m/e 366 31398 (calcd for $C_{23}H_{42}O_3$, 366.31340)] and 14 [83% yield, ^{1}H NMR ($CDCl_3$) δ 0.8-1 1 (3H, t, J=5 Hz), 1.2-1 9 (32H, m), 2.3 (2H, t, J=7 Hz), 3 7 (4H, s, overlapping peaks), IR (max) (neat) 3430 (OH), 1740 (C=O)cm^{-1}, m/e 364.29664 (calcd for $C_{23}H_{40}O_3$, 364.29775)].



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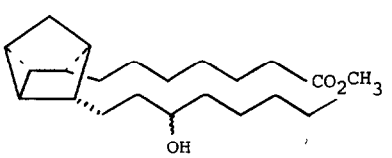

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While biological testing of these compounds is still underway and will be reported elsewhere, all substrates appear to show moderate inhibition of blood platelet aggregation.

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