6 h), 8.31-8.58 (m, 1 H). Anal. Calcd for $C_{14}H_{10}O_2$: C, 80.00; H, 4.76. Found: C, 78.30; H, 4.91.

Acknowledgment. We express appreciation to the Robert A. Welch Foundation and to the North Texas State University Faculty Research Fund for support of this investigation.

Registry No. **1a**, 4652-27-1; **1b**, 87937-54-0; **1c**, 40685-41-4; **2a**, 79-36-7; **2b**, 2912-62-1; **2c**, 525-06-4; **2d**, 20452-67-9; **2e**, 7623-09-8; **3c**, 87937-56-2; **4a**, 61550-09-2; **4b**, 53034-19-8; **5b**, 87937-60-8; **5c**, 87937-57-3; **6a**, 87937-61-9; **6b**, 87937-62-0; **8**, 87937-58-4; **9**, 87937-59-5; **11b**, 87937-63-1; **11c**, 87937-64-2; **11e**, 87937-65-3; **12b**, 50493-12-4; **12c**, 87937-66-4; **12e**, 21315-40-2; 2-(hydroxymethylene)cyclohexanone, 823-45-0; (*Z*)-β-(hydroxymethylene)-α-tetralone, 87937-55-1; α-tetralone, 529-34-0.

Supplementary Material Available: ^{13}C NMR spectral data for **5b,c**, **6a,b**, and **11a-e** (4 pages). Ordering information is given on any current masthead page.

Synthesis of 9-Substituted Carbacyclin Analogues

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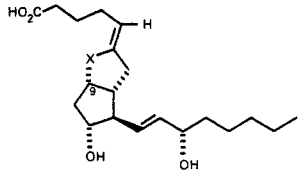
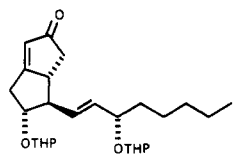
The synthesis of a series of 9-substituted carbacyclin analogues with potent platelet antiaggregatory activity is described. The key step for the formation of 9-acetylene compounds (e.g., **8d**) utilized a modification of the Schwartz procedure involving the nickel-catalyzed conjugate addition of the appropriate alkynyl aluminate to bicyclo[3.3.0]oct-1-en-3-one (**2**). It was found that 9-methylcarbacyclin (**8b**) could be prepared by a similar procedure. In addition, a novel alternative to the Wittig reaction for introducing the carbacyclin upper side chain in base-sensitive substrates was developed which involves the addition of the dianion of 6-((*tert*-butyldimethylsilyl)oxy)hexanoic acid to the appropriate ketone (e.g., **6f** or **2**) followed by decarboxylative dehydration of the resulting β-hydroxy acid.

Introduction

The potent biological activity of prostacyclin (PGI_2, **1a**),[1]



1a X = O
1b X = CH_2



2

coupled with its inherent instability ($t_{1/2}$ = 3 min at 37 °C)[2] has sparked an intense search for chemically stable analogues with similar antithrombotic properties.[3] One of the most promising of these prostacyclin mimics is carbacyclin (6a-carbaprostaglandin I_2, **1b**)[4,5] which has been shown to have a very similar biological profile to PGI_2.[6] As part of a carbacyclin analogue program we had occasion to prepare a number of 9-substituted compounds. Some of the interesting chemical and biological results of this study are described herein. In particular, the conjugate addition of alkynyl groups to a bicyclo[3.3.0]oct-1-en-3-one system was investigated, and a novel method was discovered for introducing the upper side chain.

Results and Discussion

The starting material for a host of 9-substituted carbacyclin analogues is the optically active bicyclo[3.3.0]-octenone **2**, readily available in three steps (Scheme I) from the well-known lactone **3**.[4] We found that the procedure of Schwartz[7] was an excellent method for introducing the pentynyl side chain. Thus when 1-pentyne was treated with 1 equiv of *n*-butyllithium (to generate 1-lithiopentyne) followed by 1 equiv of diethylaluminum chloride (to form the aluminum complex), then cannulated into a 1:1 mixture of a catalytic amount of nickel 2,4-pentanedionate ($Ni(acac)_2$) and diisobutylaluminum hydride (Dibah), and subsequently treated with bicyclo[3.3.0]octenone **2**, a 64% yield of the desired adduct **6a** (see Scheme II) was obtained. The upper side chain was then introduced in the normal manner.[4] Treatment with 5 equiv of (4-carboxybutyl)triphenylphosphorane in dimethyl sulfoxide (Me_2SO) at 40 °C furnished the olefin mixture **7a** in 70% yield. Finally, tetrahydropyranyl ether hydrolysis with 6:3:2 acetic acid–water–tetrahydrofuran at 40 °C for 3 h afforded the desired analogue 9-(1′-pentynyl)carbacyclin (**8a**) (57% yield) along with its corresponding 5*E* isomer **9a** (39% yield).[8]

(1) (a) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. *Nature (London)* **1976**, *263*, 663. (b) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915. (c) Vane, J. R.; Bergstrom, S. "Prostacyclin"; Raven Press: New York, 1979.

(2) Moncada, S.; Vane, J. R. *J. Med. Chem.* **1980**, *23*, 591.

(3) Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751 (and references therein).

(4) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954 (and references therein).

(5) 6a-Carba-PGI_2 has also been called 9(*O*)-methanoprostacyclin and carboprostacyclin as well as carbacyclin.

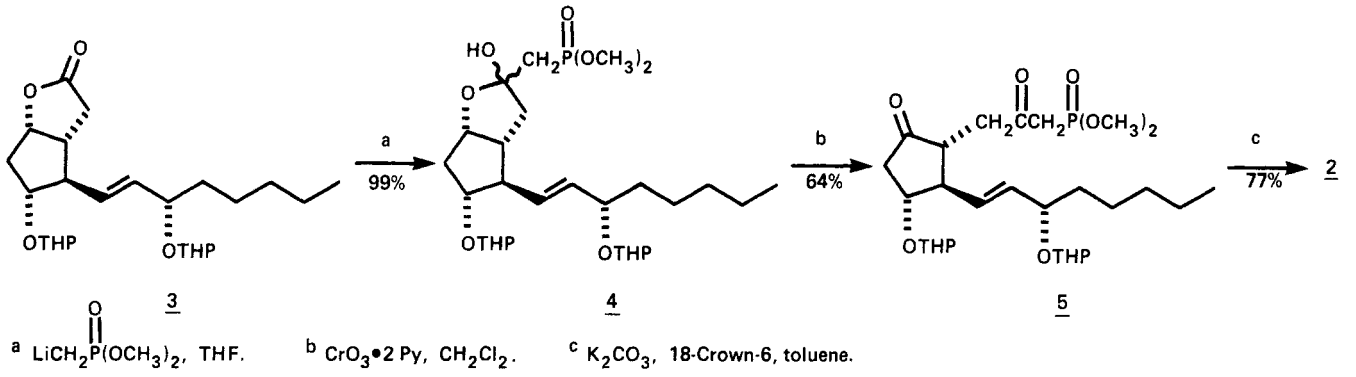
(6) (a) Whittle, B. J. R.; Moncada, S.; Whiting, F.; Vane, J. R. *Prostaglandins* **1980**, *19*, 605. (b) Aiken, J. W.; Shebuski, R. J. *Ibid.* **1980**, *19*, 629.

(7) (a) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (b) Hansen, R. T.; Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2244.

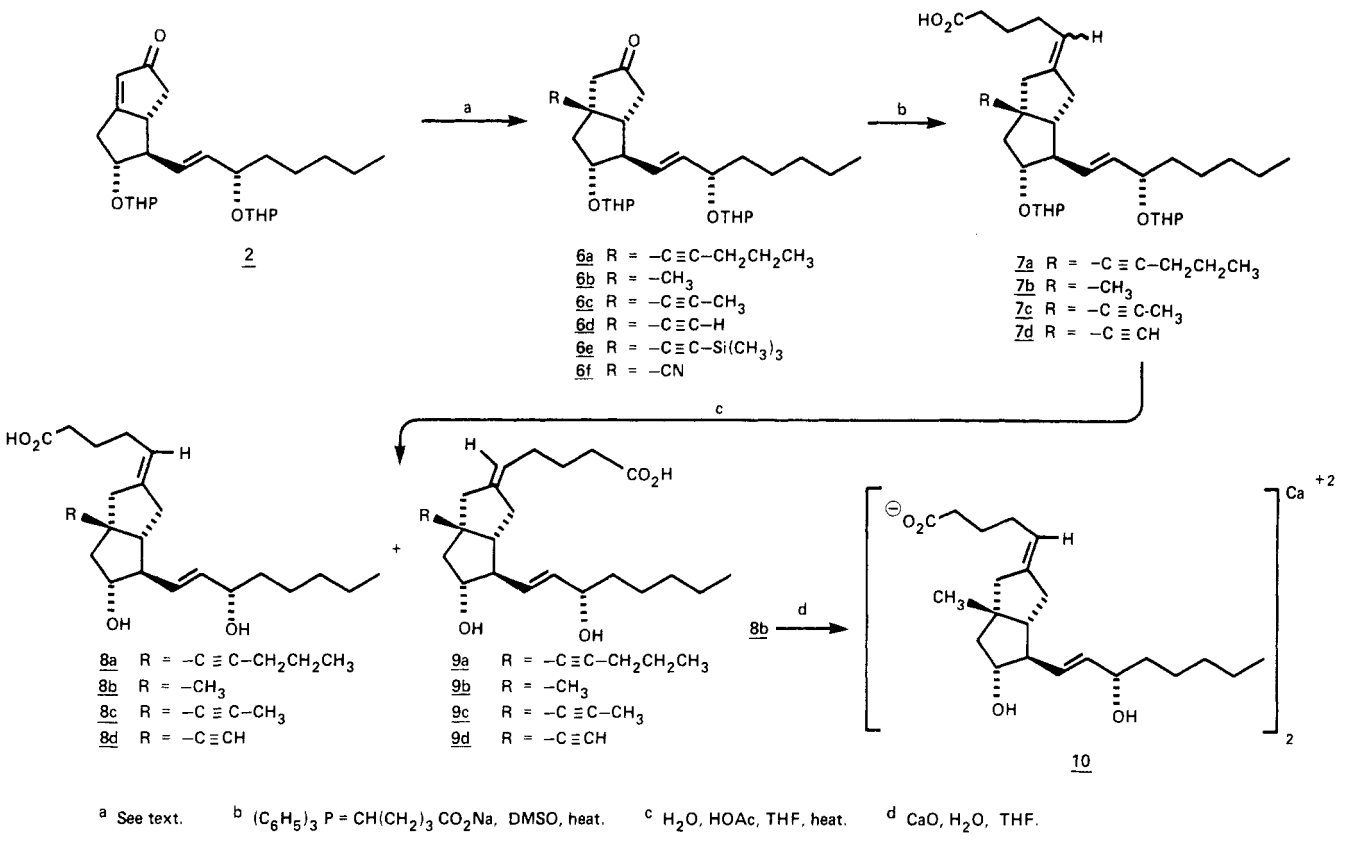
(8) Initial assignment of stereochemistry at C-5 was based upon analogy with carbacyclin and other carbacyclin analogues wherein the "natural" stereoisomer, i.e., 5*Z* in the 9-substituted series described herein, is the more polar isomer and the "unnatural" (i.e., 5*E* isomer) is the less polar isomer on TLC. The double bond isomers at C-5 can be separated either at the acid bis(THP) ether stage (compound **7**) on acid-washed silica gel or else by HPLC at the acid diol stage (compounds **8** and **9**) using a solvent system containing acetic acid. In each case the initial structural assignments were corroborated by the biological results (see Table I).

0022-3263/83/1948-5341$01.50/0

Scheme I[4]



Scheme II

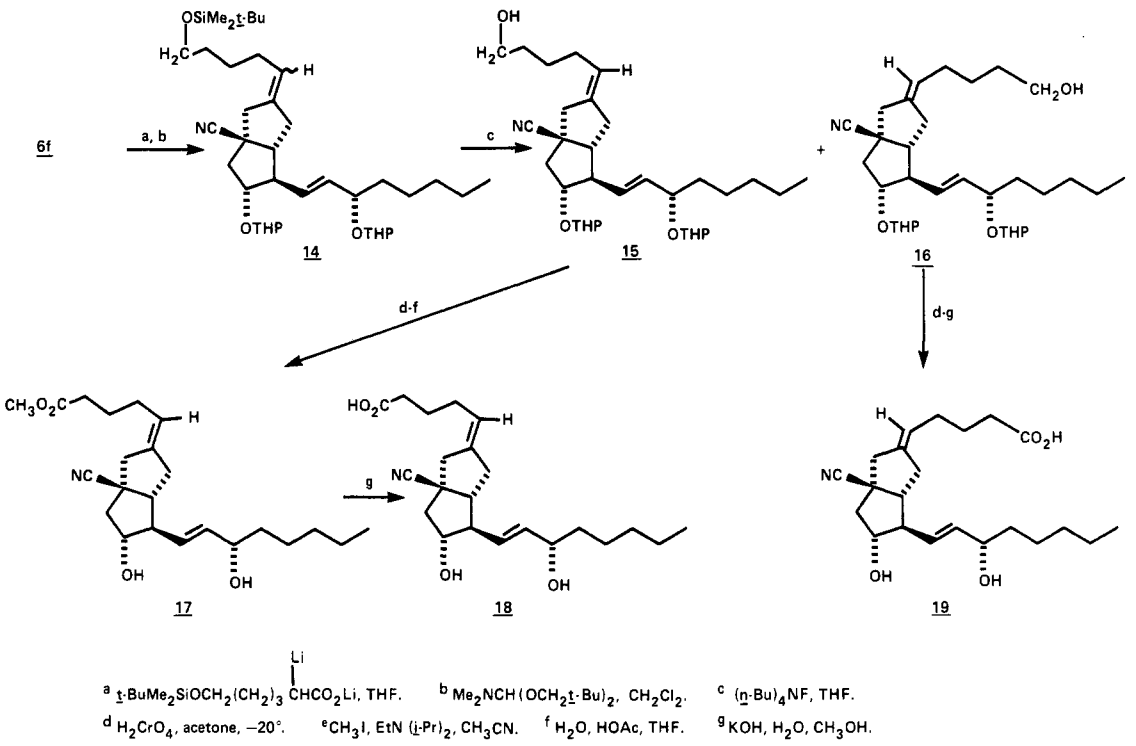


When we attempted to apply this procedure to the synthesis of the propynyl ketone **6c** some unusual results were obtained. In an attempt to generate 1-lithiopropyne, 1-(trimethylsilyl)-1-propyne was treated with 1 equiv of methyllithium in diethyl ether and stirred at room temperature for several hours. The resulting suspension was then treated with diethylaluminum chloride, $Ni(acac)_2$, Dibah, and enone **2** as previously described for the synthesis of **6a**. However, the only isolable product (68% yield) turned out to be the methyl ketone **6b**. We saw no evidence for the formation of **6c** or of products resulting from 1,2-addition of methyllithium to enone **2**. Ketone **6b** prepared by this route was identical in all respects with a sample prepared in 96% yield by addition of lithium dimethyl cuprate to bicyclo[3.3.0]octenone **2**. Compound **6b** can be converted to 9-methylcarbacyclin (**8b**) via the intermediacy of olefin mixture **7b**[8] in overall 40–45% yield. It was found that the rate of the Wittig reaction **6b** → **7b** can be dramatically increased by employing tetrahydrofuran (THF) as cosolvent. Thus whereas the reaction requires 48 h in Me_2SO, in 6:1 DMSO–THF the reaction is complete in 5 h. For the purposes of obtaining easily characterizable material, acid **8b** was converted to the solid derivative **10** (9-methylcarbacyclin calcium salt).

Apparently the methyllithium fails to react with 1-(trimethylsilyl)-1-propyne in diethyl ether and so is available to react with enone **2**. Not unexpectedly, in the absence of diethylaluminum chloride and nickel catalysis, enone **2** reacts with methyllithium exclusively at the ketone (1,2-addition). In the presence of $Ni(acac)_2$/Dibah (1:1) and an excess of methyllithium, a 3:1 ratio of 1,2- to 1,4-addition to enone **2** was obtained. When methyllithium was treated with 1 equiv of diethylaluminum chloride and subsequently with compound **2** no reaction took place until a catalytic amount of 1:1 $Ni(acac)_2$–Dibah was added. Thereupon exclusively 1,4-addition to give ketone **6b** was observed demonstrating that both the diethylaluminum chloride and nickel catalysis are necessary for the conjugate addition of the methyllithium.

When THF was substituted for diethyl ether in the methyllithium-promoted cleavage of the trimethylsilyl group to form 1-lithiopropyne, the THF removed under

Scheme III



[a] t-BuMe$_2$SiOCH$_2$(CH$_2$)$_3$CHCO$_2$Li, THF. [b] Me$_2$NCH(OCH$_2$t-Bu)$_2$, CH$_2$Cl$_2$. [c] (n-Bu)$_4$NF, THF. [d] H_2CrO_4, acetone, −20°. [e] CH_3I, EtN (i-Pr)$_2$, CH_3CN. [f] H_2O, HOAc, THF. [g] KOH, H_2O, CH_3OH.

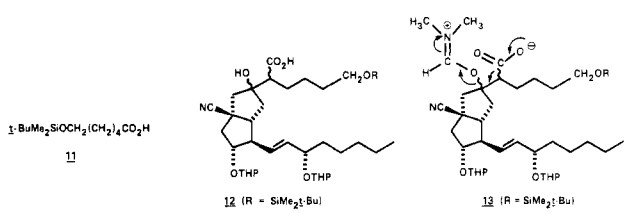
reduced pressure, diethyl ether added, and the reaction with compound **2** run as previously described for the conversion of **2** to **6a**, the desired propynyl ketone **6a** was produced in 67% yield. It was necessary to perform the nickel-catalyzed conjugate addition in diethyl ether as solvent because substantially lower yields are obtained in THF.[7] Compound **6c** was converted into 9-(1′-propynyl)carbacyclin (**8c**) by Wittig reaction with (4-carboxybutyl)triphenylphosphorane followed by THP protecting group hydrolysis.

This modification of the Schwartz procedure is particularly useful for the conjugate addition of acetylene to an enone. Previously, Schwartz[7] had used the (trimethylsilyl)acetylide reagent generated from deprotonation of (trimethylsilyl)acetylene.[9] Holmes and Walton have shown that bis(trimethylsilyl)acetylene (BTMSA) can be selectively monodesilylated in THF (but not in diethyl ether) by treatment with 1 equiv of methyllithium.[10] We found that treatment of BTMSA with methyllithium (1 equiv) in THF, followed by removal of the THF under reduced pressure and addition of diethyl ether, and followed by treatment with diethylaluminum chloride (1 equiv), a catalytic amount of 1:1 Ni(acac)$_2$–Dibah, and finally enone **2** afforded the (trimethylsilyl)ethynyl ketone **6e** in 83% yield. The trimethylsilyl group in **6e** was readily cleaved with potassium fluoride dihydrate in dimethylformamide[11] to give the ethynyl ketone **6d** (69% from enone **2**). Wittig reaction and protecting group removal afforded 9-ethynylcarbacyclin (**8d**) in 51% yield along with a 23% yield of the corresponding 5*E* isomer **9d**.[8]

Since there are relatively few methods for the introduction of an acetylene group into an enone, this simple modification of the Schwartz procedure utilizing commercially available reagents should find wide application in synthesis.

Probably due to the strain of the bicyclo[3.3.0]octenone system, compound **2** reacted readily with cyanide under mild conditions to give the cyano ketone **6f**. This hydrocyanation of the acid- and base-sensitive enone **2** was achieved in 57% yield using acetone cyanohydrin, potassium cyanide, and 18-crown-6 in toluene at room temperature.[12] Addition of the upper side chain was a more serious problem. Not surprisingly, attempted Wittig reactions of ketone **6f** with (4-carboxybutyl)triphenylphosphorane lead instead to β-elimination of cyanide to regenerate enone **2** which rapidly decomposed under the conditions of the Wittig reaction. Attempted addition of the sulfoximine reagent successfully employed by Morton in his carbacyclin synthesis[13] was complicated by competitive attack at the nitrile group. Thus it was necessary to find a new method for this transformation.

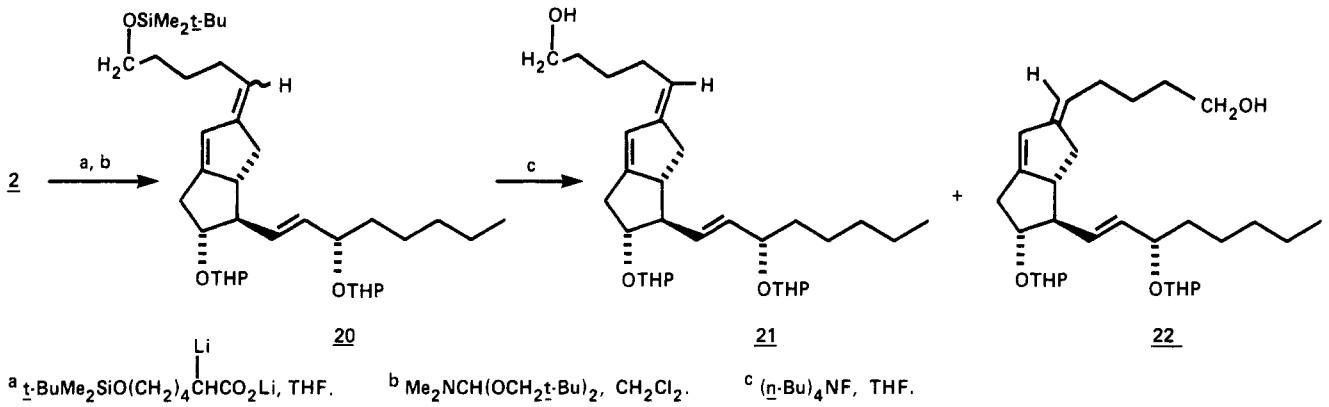
The problem was solved by a two-step procedure involving addition of a carboxylic acid dianion followed by decarboxylative dehydration. The desired side chain precursor, 6-((*tert*-butyldimethylsilyl)oxy)hexanoic acid (**11**), was conveniently prepared in a one-pot procedure



(66% yield) by treatment of ε-caprolactone with sodium hydroxide to hydrolyze the lactone, silylation with an excess of *tert*-butyldimethylsilyl chloride, and then hydrolysis of the silyl ester with more sodium hydroxide. Addition of enone **2** to the dianion of **11** (formed from treatment of **11** with 2 equiv of lithium diisopropylamide) afforded β-hydroxy acid **12**. Without purification hydroxy acid **12**

(9) Krüerke, U. *J. Organomet. Chem.* **1970**, *21*, 83.
(10) Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H.; Akinde, B.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 840.
(11) Corey, E. J.; Fleet, G. W. J.; Kato, M. *Tetrahedron Lett.* **1973**, 3963.
(12) Liotta, C. L.; Dabdoub, A. M.; Zalkow, L. H. *Tetrahedron Lett.* **1977**, 1117.
(13) Morton, D. R.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880.

Scheme IV



was treated with dimethylformamide dineopentyl acetal[14a] in methylene chloride at room temperature to give, presumably via an E2-type fragmentation of zwitterionic intermediate **13**,[15] olefin **14** (see Scheme III) in overall 50% yield from **2**. The decarboxylative dehydration of hydroxy acids with formamide acetals[16] to give olefins has been reported by several groups.[14]

Treatment of olefin mixture **14** with fluoride ion (Scheme III) afforded an easily separated mixture of alcohols **15** (35%) and **16** (57%). Alcohol **15** was converted to ester **17** in 75% yield by Jones oxidation, esterification, and THP hydrolysis. Hydroxide-mediated ester hydrolysis of **17** furnished 9-cyanocarbacyclin (**18**) in 89% yield. Similarly alcohol **16** was converted to acid **19**, the 5*E* isomer of **18**, in 68% yield.

This methodology also worked well for the introduction of the upper side chain into the base sensitive enone **2** for which other methods failed. Treatment of the dilithio anion of 6-((*tert*-butyldimethylsilyl)oxy)hexanoic acid with **2** followed by decarboxylative dehydration of the resulting β-hydroxy acid afforded diene **20** (Scheme IV) in overall 60% yield. Fluoride-mediated silyl ether protecting group hydrolysis afforded alcohols **21** (52%) and **22** (30%). Decarboxylative dehydration of hydroxy acids with formamide acetals has been used only sparingly in synthesis (and mostly for the formation of dienes).[17] Our experience indicates that the carboxylic acid dianion/decarboxylative dehydration procedure is a mild, useful alternative to the Wittig reaction and should have wider applicability in organic synthesis.

As indicated in Table I the (5*Z*)-9-substituted carbacyclin analogues are all effective at inhibiting ADP-induced human platelet aggregation.[18] In particular, 9-cyanocarbacyclin (**18**), 9-ethynylcarbacyclin (**8d**), and 9-(1′-propynyl)carbacyclin (**8c**) are all more active than carbacyclin (**1b**) at inhibiting platelet aggregation. The acetylenic analogues **8c** and **8d** are especially interesting, being chemically stable compounds that are approximately twice as potent as prostacyclin on platelets. Further investigations of 9-substituted carbacyclin analogues will be reported in due course.

Table I. In Vitro Inhibition of ADP-Induced Human Platelet Aggregation[a]

compd	ID_{50}, ng/mL
prostacyclin (**1a**)	2
carbacyclin (**1b**)	20
(5*Z*)-9-(1′-pentynyl)carbacyclin (**8a**)	100
(5*E*)-9-(1′-pentynyl)carbacyclin (**9a**)	>1000
(5*Z*)-9-methylcarbacyclin (**8b**)	60
(5*E*)-9-methylcarbacyclin (**9b**)	≥1000
(5*Z*)-9-(1′-propynyl)carbacyclin (**8c**)	1
(5*E*)-9-(1′-propynyl)carbacyclin (**9c**)	>1000
(5*Z*)-9-ethynylcarbacyclin (**8d**)	1
(5*E*)-9-ethynylcarbacyclin (**9d**)	≥1000
(5*Z*)-9-cyanocarbacyclin (**18**)	10
(5*E*)-9-cyanocarbacyclin (**19**)	≥1000

[a] See ref 18.

Experimental Section[19]

(3′*S*)-1β-(1′-Pentynyl)-7α-[(tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]bicyclo[3.3.0]octan-3-one (6a). A solution of 1.96 g (28.8 mmol) of 1-pentyne in 50 mL of ether at −35 °C was treated with 18 mL (29 mmol) of 1.6 M *n*-butyllithium in hexane. The resulting white suspension was stirred for 10 min at −35 °C, treated with 14 mL (29 mmol) of 25% diethylaluminum chloride in hexane, stirred at 0 °C for 1 h, and then cannulated into a −5 °C solution of 0.74 g (2.88 mmol) of nickel 2,4-pentanedionate ($Ni(acac)_2$) and 2.6

(14) (a) Rüttimann, A.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, *58*, 1450. (b) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, 1545. (c) Mulzer, J.; Kuhl, U.; Brüntrup, G. *Tetrahedron Lett.* **1978**, 2953.

(15) Mulzer, J.; Brüntrup, G. *Tetrahedron Lett.* **1979**, 1909.

(16) A review of the chemistry of formamide acetals has been published: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.

(17) (a) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Kido, F.; Noda, Y.; Maruyama, T.; Kabuto, C.; Yoshikoshi, A. *J. Org. Chem.* **1981**, *46*, 4264. (c) Mulzer, J.; Brüntrup, G.; Kühl, U.; Hartz, G. *Chem. Ber.* **1982**, *115*, 3453. (d) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1982**, *65*, 2212.

(18) Biological testing was conducted at The Upjohn Company by R. R. Gorman, J. W. Aiken, C. F. Lawson, V. R. Bockstanz, and M. A. Wynalda.

(19) All analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (solids). Mass spectra were recorded at high or low resolution for derivatized (Me_3Si) or underivatized compounds at 70 eV. The ^1H NMR spectra were obtained on a Varian A-60D spectrometer operating at 60 MHz, a Varian HFT-80 spectrometer operating at 80 MHz, or a Varian EM 390 spectrometer operating at 90 MHz of chloroform-*d* solutions. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Thin-layer chromatography (TLC) was conducted with Analtech (Uniplates) glass plates precoated with silica gel GF (250 nm). The solvent system used for determining the R_f of the 9-substituted carbacyclin acids (i.e., **8**, **9**, **18**, and **19**) is the organic layer from an equilibrated mixture of 9:2:5:10 ethyl acetate–acetic acid–cyclohexane–water. The TLC plates were visualized first by UV light (Mineralight UVS-11) and then by spraying with 50% aqueous sulfuric acid followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck, 70–230 mesh). Acid washed silica gel was Mallinckrodt CC-4. HPLC silica gel utilized Lobar prepacked size B columns (E. Merck, 40–63 μm). Brine refers to a saturated aqueous solution of NaCl. THF was dried by distillation under nitrogen from sodium/benzophenone ketyl. All other solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). Diisopropylamine was dried by distillation under nitrogen from calcium hydride. Nickel 2,4-pentanedionate ($Ni(acac)_2$) was purified by azeotropic removal of water from the dihydrate with toluene followed by drying in vacuo at 100 °C. All other reagents were used as purchased and were reagent grade where available. All reactions were degassed and were done under an inert atmosphere.

mL (2.6 mmol) of 1.0 M hexane solution of diisobutylaluminum hydride (Dibah) in 50 mL of ether. The resulting black suspension was treated with 5.65 g (13.1 mmol) of (3-*S*)-7α-[(tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]-bicyclo[3.3.0]oct-1-en-3-one (**2**)[4] in 30 mL of ether, stirred for 3 h at −5 °C, and cannulated into cold saturated aqueous NaH_2PO_4. The layers were separated and the aqueous layer extracted with additional ether. The combined organic fractions were washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue chromatographed on silica gel euted with 20% ethyl acetate in hexane to give 4.17 g (64%) of **6a** as an oil: R_f 0.32 (in 20% ethyl acetate in hexane); NMR δ 0.94 (t, J = 5 Hz, 6 H), 1.07–3.22 (m, 32 H), 3.22–4.4 (m, 6 H), 4.64 (br s, 2 H), 5.1–5.82 (m, 2 H); IR (film) 1745, 1455, 1340, 1200, 1155, 1130, 1115, 1075, 1035, 1020, 975, 870 cm^{-1}. Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.36; H, 9.60.

(3′*S*)-1β-Methyl-7α-[(tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]bicyclo-[3.3.0]octan-3-one (6b). (a) Cuprate Procedure. A suspension of 2.70 g (14.2 mmol) of anhydrous copper iodide in 100 mL of ether at −20 °C was treated dropwise with 20.0 mL (28 mmol) of 1.4 M ethereal methyllithium–lithium bromide complex. The resulting solution was stirred for 15 min at −20 °C, treated over 2.5 h at −20 °C with a solution of 2.00 g (4.62 mmol) of enone **2** in 100 mL of ether, stirred for another 2.5 h at −20 °C, and added to 200 mL of 1 M aqueous ammonium chloride. The layers were separated and the aqueous layer extracted with additional ether. The combined ether portions were washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue chromatographed on silica gel eluted with 25% ethyl acetate in hexane to give 2.00 g (96%) of ketone **6b** as a colorless oil: R_f 0.26 (in 25% ethyl acetate in hexane); NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.06–2.85 (m including 3 H singlet at δ 1.18, 31 H), 3.20–4.43 (m, 6 H), 4.70 (br s, 2 H), 5.2–5.9 (m, 2 H); IR (film) 1745, 1665, 1200, 1130, 1110, 1075, 1035, 1020, 980, 870 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.17; H, 9.77.

(b) Aluminate Procedure. A solution of 0.98 mL (6.6 mmol) of 1-(trimethylsilyl)-1-propyne in 10 mL of ether was treated with 4.8 mL (6.7 mmol) of ethereal 1.4 M methyllithium–lithium bromide complex, stirred for 3 h at room temperature, cooled to 0 °C, and treated with 3.2 mL (6.6 mmol) of 25% diethylaluminum chloride in hexane. The resulting white suspension was stirred for 1 h at 0 °C and then cannulated into a −10 °C solution of 0.17 g (0.66 mmol) of $Ni(acac)_2$ and 0.6 mL (0.6 mmol) of 1 M Dibah in 10 mL of ether. The resulting black solution was treated with 1.3 g (3.0 mmol) of enone **2** in 15 mL of ether, stirred for 3 h at −5 °C, added to 100 mL of cold saturated aqueous NaH_2PO_4, and extracted with ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel eluted with 15% ethyl acetate in hexane to give 0.911 g (68%) of **6b**.

(3′*S*)-1β-(1′-Propynyl)-7α-[(tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]bicyclo[3.3.0]octan-3-one (6c). A solution of 0.98 mL (6.6 mmol) of 1-(trimethylsilyl)-1-propyne in 10 mL of THF was treated dropwise with 4.8 mL (6.7 mmol) of ethereal 1.4 M methyllithium–lithium bromide complex, stirred for 3 h at room temperature, cooled to 0 °C, and the THF was removed under reduced pressure. The oily residue was taken up in 10 mL of ether at 0 °C and treated with 3.2 mL (6.6 mmol) of 25% diethylaluminum chloride in hexane. The resulting white suspension was stirred for 1 h at 0 °C and then cannulated into a −10 °C solution of 0.17 g (0.66 mmol) of $Ni(acac)_2$ and 0.6 mL (0.6 mmol) of 1 M Dibah in 10 mL of ether. The resulting black solution was treated with 1.3 g (3.0 mmol) of enone **2** in 15 mL of ether, stirred 3 h at −5 °C, added to 100 mL of cold saturated aqueous NaH_2PO_4, and extracted with ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel eluted with 15% ethyl acetate in hexane to give 0.947 g (67%) of **6c** as an oil: R_f 0.28 (in 20% ethyl acetate in hexane); NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.0–2.8 (m including 3 H singlet at δ 1.77, 31 H), 3.3–3.6 (m, 2 H), 3.6–4.4 (m, 4 H), 4.7 (br s, 2 H), 5.1–5.8 (m, 2 H); IR (film) 2925, 2850, 1745, 1445, 1200, 1120, 1030, 1020, 980, 865, 815 cm^{-1}. Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.23; H, 9.32.

(3′*S*)-1β-(Ethynyl-7α-[(tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]bicyclo-[3.3.0]octan-3-one (6d). A solution of 7.5 mL (33 mmol) of bis(trimethylsilyl)acetylene in 50 mL of THF was treated with 24 mL (33 mmol) of ethereal 1.4 M methyllithium–lithium bromide, stirred for 3 h at room temperature, put under vacuum to remove the THF, cooled to 0 °C, treated with 50 mL of ether and then with 16 mL (33 mmol) of 25% diethylaluminum chloride in hexane, stirred for 1 h at 0 °C, and cannulated into a −10 °C solution of 0.80 g (3.1 mmol) of $Ni(acac)_2$ and 3.0 mL (3.0 mmol) of 1 M Dibah (in hexane) in 50 mL of ether. The resulting black solution was treated with 6.1 g (14.1 mmol) of enone **2** in 75 mL of ether, stirred for 3 h at −5 °C, added to 500 mL of saturated aqueous NaH_2PO_4, and extracted with ether. The ether extracts were washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel eluted with 15% ethyl acetate in hexane to give 6.2 g (83%) of ketone **6e** as a light brown oil (R_f 0.25 in 15% ethyl acetate in hexane); NMR δ 0.09 (s, 9 H), 0.89 (t, J = 5 Hz, 3 H), 1.04–3.0 (m, 28 H), 3.28–4.4 (m, 6 H), 4.66 (br s, 2 H), 5.1–5.8 (m, 2 H); IR (film) 2160, 1745, 1250, 1200, 1125, 1075, 1035, 1020, 980 cm^{-1}.

Without further purification 1.00 g (1.88 mmol) of ketone **6e** was dissolved in 30 mL of dimethylformamide, treated with 0.35 g (3.72 mmol) of potassium fluoride dihydrate, stirred at 0 °C for 4 h, diluted with brine, and extracted with 1:1 hexane–ether. The combined organic extracts were washed with water and brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel eluted with 20% ethyl acetate in hexane to give 0.72 g (83%) of **6d** as a pale yellow oil: R_f 0.27 (in 20% ethyl acetate in hexane); NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.04–3.0 (m including 1 H singlet at δ 2.25, 29 H), 3.26–4.42 (m, 6 H), 4.67 (br s, 2 H); 5.05–5.8 (m, 2 H); IR (film) 3285, 2110 (weak), 1750, 1200, 1155, 1130, 1075, 1035, 1020, 995, 975 cm^{-1}. Anal. Calcd for $C_{28}H_{42}O_5$: C, 73.33; H, 9.23. Found: C, 73.15; H, 9.63.

(3′*S*)-1β-Cyano-7α-[(tetrahydropyran-2-yl)oxy]-6β-[3′-[(tetrahydropyran-2-yl)oxy]-*trans*-1′-octenyl]bicyclo-[3.3.0]octan-3-one (6f). A solution of 1.43 g (3.31 mmol) of enone **2**, 0.51 g (3.9 mmol) of 18-crown-6, 0.43 g (6.6 mmol) of potassium cyanide, and 0.36 mL (3.94 mmol) of acetone cyanohydrin in 20 mL of toluene was stirred at ambient temperature for 18 h, added to 100 mL of water, and extracted with ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel eluted with 2:1 hexane–ethyl acetate to give 0.86 g (57%) of **6f** as a pale yellow oil: R_f 0.31 (in 2:1 hexane–ethyl acetate); NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.08–3.24 (m, 28 H), 3.24–4.47 (m, 6 H), 4.67 (br s, 2 H), 5.3–5.9 (m, 2 H); IR (film) 2230, 1750, 1665, 1200, 1155, 1125, 1075, 1035, 1020, 975 cm^{-1}. Anal. Calcd for $C_{27}H_{41}O_5N$: C, 70.56; H, 8.99; N, 3.05. Found: C, 70.46; H, 8.93; N, 2.99%.

(5*Z*)-9β-(1′-Pentynyl)-6a-carbaprostaglandin I_2 (8a) and (5*E*)-9β-(1′-Pentynyl)-6a-carbaprostaglandin I_2 (9a). A solution of 86 mmol of sodium methylsulfinylmethide (prepared from 3.62 g of a 57% sodium hydride dispersion and 260 mL of Me_2SO) was cooled to 15 °C, treated with 19.1 g (43 mmol) of (4-carboxybutyl)triphenylphosphonium bromide, stirred at 15 °C for 20 min, treated with 3.90 g (7.79 mmol) of ketone **6a** in 40 mL of Me_2SO, stirred at 40 °C for 88 h, cooled to 0 °C, treated with 30 mL of water, stirred for 2 h at 0 °C, acidified with a solution of 5.5 mL of H_2SO_4 in 200 mL of 7:3 water–brine, and extracted with ether. The ether extracts were washed several times with water and then with brine and were dried ($MgSO_4$). The solvents were removed under reduced pressure and the residue was chromatographed on acid-washed silica gel eluted with 15% ethyl acetate in hexane to give 3.20 g (70%) of acid mixture **7a** as an oil (R_f 0.46 in 64:35:1 hexane–ethyl acetate–acetic acid).

Without further purification, 0.63 g (1.08 mmol) of acid **7a** was heated at 45 °C in a solution of 4 mL of THF, 6 mL of water, and 12 mL of glacial acetic acid. After 3 h the solution was cooled and partitioned between brine and 3:2 ethyl acetate–hexane. The organic portion was dried (Na_2SO_4) and the solvent removed under reduced pressure (using a toluene azeotrope to remove any re-

maining acetic acid). The crude product was chromatographed on HPLC silica gel eluted with 1000:40:5 chloroform–methanol–acetic acid to give 0.26 g (58%) of acid **8a** as a colorless oil (R_f 0.43) and 0.17 g (38%) of acid **9a** as a colorless oil (R_f 0.44).

8a: NMR δ 0.95 (t, J = 9 Hz, 6 H), 1.1–3.0 (m, 26 H), 3.7–4.3 (m, 2 H), 4.98–5.68 (m, 3 H), 5.99 (br s, 3 H); IR (film) 3335, 2235 (weak), 1710, 1455, 1430, 1340, 1330, 1245, 1095, 1075, 970 cm^{-1}; mass spectrum, calcd for $C_{35}H_{64}O_4Si_3$ [M^+ of tris(trimethylsilyl) derivative], m/e 632.4088; found, m/e 632.4112; calcd for $C_{34}H_{61}O_4Si_3$ [$M^+ - CH_3$ of tris(trimethylsilyl) derivative], m/e 617.3878; found, m/e 617.3859.

9a: NMR δ 0.5–3.0 (m, 32 H), 3.65–4.3 (m, 2 H), 5.08–6.2 (m including 3 H br s at δ 5.8, 6 H); IR (film) 3340, 2235 (weak), 1710, 1455, 1430, 1340, 1330, 1250, 1240, 1085, 970 cm^{-1}; mass spectrum, calcd for $C_{34}H_{61}O_4Si_3$ [$M^+ - CH_3$ of tris(trimethylsilyl) derivative], m/e 617.3878; found, m/e 617.3872.

(5*Z*)-9β-Methyl-6a-carbaprostaglandin I_2 (8b) and (5*E*)-9β-Methyl-6a-carbaprostaglandin I_2 (9b). A solution of 17 mmol of sodium methylsulfinylmethide (prepared from 0.81 g of a 50% sodium hydride dispersion and 66 mL of Me_2SO) was cooled to 15 °C, treated with 4.20 g (9.60 mmol) of (4-carboxybutyl)triphenylphosphonium bromide, stirred for 20 min, treated with 0.80 g (1.78 mmol) of ketone **6b** in 12 mL of THF, stirred for 5 h at 45 °C, cooled to 0 °C, treated with 6 mL of water, stirred for 1 h, acidified with a solution of 5 mL of H_2SO_4 in 100 mL of 1:1 water–brine, and extracted with ether. The ether extracts were washed several times with water and then with brine and were dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was chromatographed on acid-washed silica gel eluted with 20% ethyl acetate in hexane to give 0.932 g (98%) of acid mixture **7b** as an oil (R_f 0.38 in 65:34:1 hexane–ethyl acetate–acetic acid).

Without further purification, 0.75 g (1.41 mmol) of acid **7b** was heated at 45 °C in a solution of 5 mL of THF, 7.5 mL of water, and 15 mL of glacial acetic acid. After 3 h the solution was cooled and partitioned between brine and 3:2 ethyl acetate–hexane. The organic portion was dried (Na_2SO_4) and the solvent removed under reduced pressure (using a toluene azeotrope to remove any remaining acetic acid). The crude product was chromatographed on HPLC silica gel eluted with 1000:40:5 chloroform–methanol–acetic acid to give 0.24 g (47%) of acid **8b** as a colorless oil (R_f 0.25) and 0.23 g (45%) of acid **9b** as a colorless oil (R_f 0.27).

8b: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.02–2.8 (m including 3 H singlet at δ 1.08, 25 H), 3.5–4.35 (m, 2 H), 5.0–5.7 (m, 3 H), 6.05 (br s, 3 H); IR (film) 3340, 2660, 1710, 1240, 1205, 1175, 1130, 1075, 1055, 1020, 970 cm^{-1}; mass spectrum, calcd for $C_{30}H_{57}O_4Si_3$ [$M^+ - CH_3$ of tris(trimethylsilyl) derivative], m/e 565.3564; found, m/e 565.3552.

9b: NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.06 (s, 3 H), 1.1–2.6 (m, 22 H), 3.5–4.3 (m, 2 H), 5.0–5.7 (m, 3 H), 5.93 (br s, 3 H); IR (film) 3340, 2660, 1710, 1300, 1240, 1175, 1130, 1075, 1055, 1020, 970 cm^{-1}; mass spectrum, calcd for $C_{30}H_{57}O_4Si_3$ [$M^+ - CH_3$ of tris(trimethylsilyl) derivative], m/e 565.3564; found, m/e 565.3541.

(5*Z*)-9β-Methyl-6a-carbaprostaglandin I_2, Calcium Salt (10). A suspension of 350 mg (0.96 mmol) of acid **8b**, 23.6 mg (0.42 mmol) of calcium oxide, 5 mL of water, and 4 mL of THF was heated for 20 min at 50 °C and filtered, and the solvents were removed under reduced pressure. The resulting foam was dissolved in 4 mL of THF and then added dropwise to 50 mL of ether. The resulting suspension was stirred for 15 min, then filtered (rinsing with ether) to give 265 mg (82%) of calcium salt **10** as a white solid: mp 101–108 °C; IR (mull) 3330, 1670, 1555, 1455, 1345, 1310, 1270, 1075, 1020, 970 cm^{-1}. Anal. Calcd for $C_{44}H_{70}O_8Ca$: C, 68.89; H, 9.20; Ca, 5.23. Found: C, 68.55; H, 8.94; Ca, 5.29.

(5*Z*)-9β-(1′-Propynyl)-6a-carbaprostaglandin I_2 (8c) and (5*E*)-9β-(1′-Propynyl)-6a-carbaprostaglandin I_2 (9c). In a similar manner to the conversion of ketone **6b** to acid mixture **7b** and then to (5*Z*)-9β-methyl-6a-carbaprostaglandin I_2 (**8b**) and (5*E*)-9β-methyl-6a-carbaprostaglandin I_2 (**9b**), 0.83 g (1.75 mmol) of ketone **6c** was converted to 0.47 g (48%, 65% based on recovered **6c**) of acid mixture **7c** (R_f 0.51 in 65:34:1 hexane–ethyl acetate–acetic acid) and then to 118 mg (36%) of acid **8c** as a colorless oil (R_f 0.45) and 112 mg (34%) of acid **9c** as a colorless oil (R_f 0.47). For **8c**: NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.0–2.8 (m including 3 H singlet at δ 1.78, 28 H), 3.7–4.2 (m, 2 H), 5.1–5.4 (m, 1 H), 5.4–5.6 (m, 2 H), 6.05 (br s 3 H); IR (film) 3300, 1710, 1435, 1250, 1075, 970, 915 cm^{-1}; mass spectrum, calcd for $C_{33}H_{60}O_4Si_3$ [M^+ of tris(trimethylsilyl) derivative], m/e 604.3799; found, m/e 604.3770.

9c: NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.0–2.8 (m including 3 H singlet at δ 1.78, 28 H), 3.7–4.2 (m, 2 H), 5.1–5.4 (m, 1 H), 5.4–5.7 (m, 2 H), 6.27 (br s, 3 H); IR (film) 3300, 1710, 1435, 1075, 970, 915 cm^{-1}; mass spectrum, calcd for $C_{33}H_{60}O_4Si_3$ [M^+ of tris(trimethylsilyl) derivative], m/e 604.3799; found, m/e 604.3776.

(5*Z*)-9β-Ethynyl-6a-carbaprostaglandin I_2 (8d) and (5*E*)-9β-Ethynyl-6a-carbaprostaglandin I_2 (9d). In a similar manner to the conversion of ketone **6a** to acid mixture **7a** and then to (5*Z*)-9β-(1′-pentynyl)-6a-carbaprostaglandin I_2 (**8a**) and (5*E*)-9β-(1′-pentynyl)-6a-carbaprostaglandin I_2 (**9a**), 3.81 g (8.31 mmol) of ketone **6d** was converted to 3.43 g (76%) of acid mixture **7d** (R_f 0.40 in 64:35:1 hexane–ethyl acetate–acetic acid) and then (starting with 3.00 g (5.52 mmol) of acid **7d** to 1.40 g (68%) of acid **8d** as a colorless oil (R_f 0.43) and 0.64 g (31%) of acid **9d** as a colorless oil (R_f 0.44).

For **8d**: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.07–3.1 (m including 1 H singlet at δ 2.21, 23 H), 3.7–4.4 (m, 2 H), 5.0–6.5 (m including 3 H broad singlet at δ 5.83, 6 H); IR (film) 3300, 2110, 1710, 1455, 1430, 1410, 1300, 1245, 1095, 1075, 970 cm^{-1}; mass spectrum, calcd for $C_{32}H_{58}O_4Si_3$ [M^+ of tris(trimethylsilyl) derivative], m/e 590.3643; found, m/e 590.3633.

9d: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.08–3.5 (m including 1 H singlet at δ 2.19, 23 H), 3.7–4.4 (m, 2 H), 5.07–6.8 (m including 3 H broad singlet at δ 5.90, 6 H); IR (film) 3300, 2110, 1710, 1455, 1430, 1410, 1300, 1245, 1095, 1075, 970 cm^{-1}; mass spectrum, calcd for $C_{32}H_{58}O_4Si_3$ [M^+ of tris(trimethylsilyl) derivative], m/e 590.3643; found, m/e 590.3657.

6-(*tert*-Butyldimethylsilyloxy)hexanoic Acid (11). A solution of 10.0 mL (90 mmol) of ϵ-caprolactone and 4.0 g (100 mmol) of sodium hydroxide in 100 mL of 4:1 methanol–water was stirred for 5 h and then the solvent removed under reduced pressure to give 15 g of 6-hydroxyhexanoic acid sodium salt. The crude 6-hydroxyhexanoic acid sodium salt was suspended in 300 mL of dimethylformamide, cooled to 0 °C, treated with 35 g (510 mmol) of imidazole and 39 g (260 mml) of *tert*-butyldimethylsilyl chloride, stirred for 26 h at room temperature, treated with 8 g of sodium hydroxide in 80 mL of 1:1 methanol–water, stirred for 13 h, acidified to pH 4 with aqueous hydrochloric acid, and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue chromatographed on silica gel eluted with ethyl acetate–hexane (1:9 to 1:1) to give 14.8 g (67%) of acid **11** as a pale yellow oil (R_f 0.36 in 3:1 hexane/the aqueous phase of 9:2:5:10 ethyl acetate–acetic acid–cyclohexane–water): NMR δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.2–2.0 (m, 6 H), 2.17–2.55 (m, 2 H), 3.42–3.83 (s, 2 H), 11.72 (s, 1 H); IR (film) 3040, 2740, 2660, 1715, 1255, 1100, 835, 775 cm^{-1}; mass spectrum, calcd for $C_{11}H_{23}SiO_3$ [$M^+ - CH_3$ of trimethylsilyl derivative], m/e 231.1416; found, m/e 231.1399.

2-Decarboxy-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-9β-cyano-6a-carbaprostaglandin I_2 11,15-Bis(tetrahydropyranyl) Ether (14). A solution of 8.32 mmol of lithium diisopropylamide (prepared from 1.20 mL (8.56 mmol) of diisopropylamine and 5.2 mL (8.32 mmol) of 1.6 M butyllithium (in hexane) in 40 mL of THF) at 0 °C was treated with 1.03 g (4.18 mmol) of 6-((*tert*-butyldimethylsilyl)oxy)hexanoic acid (**11**), stirred at 0 °C for 15 min and at room temperature for 1 h, cooled to 0 °C, treated with 1.70 g (3.70 mmol) of ketone **6f**, stirred at ambient temperature for 20 h, acidified with aqueous hydrochloric acid, and extracted with ether. The ether extracts were washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure to give 2.50 g of crude β-hydroxy acid **12** as a yellow oil. Without further purification 2.46 g of crude acid mixture **12** was dissolved in 30 mL of methylene chloride, treated with 5.0 mL (18 mmol) of dimethylformamide dineopentyl acetal, stirred at room temperature for 117 h, and then partitioned beween water and ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate solution and with brine and were dried ($MgSO_4$). The solvents were concentrated under reduced pressure and the residue was chromatographed on silica gel eluted with 20% ethyl acetate in hexane to give 1.2 g (50%) of olefin mixture **14** as a pale yellow oil (R_f 0.33

and 0.37 in 20% ethyl acetate in hexane): NMR δ 0.05 (s, 6 H), 0.91 (s, 12 H), 1.08–2.9 (m, 34 H), 3.25–4.40 (m, 8 H), 4.68 (br s, 2 H), 5.02–5.8 (m, 3 H); IR (film) 2230, 1670, 1255, 1200, 1125, 1100, 1080, 1035, 1020, 975, 835, 775 cm^{-1}. Anal. Calcd for $C_{38}H_{65}O_5NSi$: C, 70.87; H, 10.17. Found: C, 70.97; H, 10.12.

(5*Z*)-2-Decarboxy-2-(hydroxymethyl)-9β-cyano-6a-carbaprostaglandin I_2 11,15-Bis(tetrahydropyranyl) Ether (15) and (5*E*)-2-Decarboxy-2-(hydroxymethyl)-9β-cyano-6a-carbaprostaglandin I_2 11,15-Bis(tetrahydropyranyl) Ether (16). A solution of 1.10 g (1.71 mmol) of silyl ether **14** in 20 mL of THF at 0 °C was treated with 4.8 mL (3.6 mmol) of 0.75 M tetra-*n*-butylammonium fluoride (in THF), stirred for 18 h at ambient temperature, and partitioned between brine and ethyl acetate. The combined ethyl acetate extracts were washed with 0.5 M aqueous potassium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue chromatographed on HPLC silica gel eluted with 45% ethyl acetate in hexane to give 0.32 g (35%) of alcohol **15** as a colorless oil (R_f 0.25 in 45% ethyl acetate in hexane) and 0.52 g (57%) of alcohol **16** as a colorless oil (R_f 0.29 in 45% ethyl acetate in hexane).

15: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.05–3.0 (m, 35 H), 3.2–4.4 (m, 8 H), 4.69 (br s, 2 H), 5.1–5.9 (m, 3 H); IR (film) 3480, 2240, 1670, 1200, 1130, 1075, 1035, 1020, 975, 905, 870 cm^{-1}. Anal. Calcd for $C_{32}H_{51}O_5N$: C, 72.55; H, 9.70. Found: C, 72.66; H, 10.09.

16: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.07–3.2 (m, 35 H), 3.2–4.4 (m, 8 H), 4.67 (br s, 2 H), 5.0–5.8 (m, 3 H); IR (film) 3480, 2240, 1670, 1200, 1130, 1075, 1035, 1020, 975, 905, 870 cm^{-1}. Anal. Calcd for $C_{32}H_{51}O_5N$: C, 72.55; H, 9.70. Found: C, 72.57; H, 9.70.

(5*Z*)-9β-Cyano-6a-carbaprostaglandin I_2, Methyl Ester (17). A solution of 307 mg (0.58 mmol) of alcohol **15** in 11 mL of acetone at −20 °C was treated with 0.55 mL of Jones reagent, and the resulting suspension was stirred at −20 °C for 2 h before being quenched with 0.6 mL of 2-propanol and partitioned between brine and ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4). The solvents were removed under reduced pressure to give 0.3 g of an oil which was dissolved in 4 mL of acetonitrile at −15 °C and treated with 1.2 mL of diisopropylethylamine and 0.43 mL of methyl iodide. The resulting suspension was stirred for 18 h at ambient temperature and then partitioned between brine and ethyl acetate. The combined ethyl acetate extracts were washed with 0.5 M aqueous potassium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried (Na_2SO_4). The solvents were removed under reduced pressure to give 0.3 g of an oil which was dissolved in 14 mL of 1:2:4 THF–water–acetic acid, stirred for 3 h at 45 °C, cooled, and partitioned between brine and ethyl acetate. The combined ethyl acetate extracts were washed with saturated aqueous sodium bicarbonate and brine and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel eluted with 20% ethyl acetate in hexane to give 0.17 g (75%) of ester **17** as a colorless oil: R_f 0.25 (in 20% hexane in ethyl acetate); NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.05–3.0 (m, 22 H), 3.2–3.5 (m including 3 H singlet at δ 3.68, 7 H), 5.15–5.85 (m, 3 H); IR (film) 3400, 2230, 1740, 1675, 1435, 1315, 1250, 1230, 1200, 1170, 1135, 1100, 1075, 1020, 970 cm^{-1}; mass spectrum, calcd for $C_{29}H_{51}O_4NSi_2$ [M^+ of bis(trimethylsilyl) derivative], m/e 533.3356; found, m/e 533.3346. Anal. Calcd for $C_{23}H_{35}O_4N$: C, 70.92; H, 9.06. Found: C, 70.77; H, 9.03.

(5*Z*)-9β-Cyano-6a-carbaprostaglandin I_2 (18). A solution of 0.14 g (0.36 mmol) of ester **17**, 2.7 mL of 10% potassium hydroxide in 9:1 methanol–water, and 2.7 mL of 9:1 methanol–water was stirred for 17 h, acidified with 5 mL of 1 M aqueous hydrochloric acid, and partitioned between brine and ethyl acetate. The ethyl acetate extracts were dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was chromatographed on acid-washed silica gel eluted with 2:1 ethyl acetate–hexane to give 0.12 g (89%) of acid **18** as a colorless oil: R_f 0.29; NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.05–3.1 (m, 22 H), 3.65–4.39 (m, 2 H), 5.1–5.68 (m, 3 H), 6.05 (br s, 3 H); IR (film) 3380, 2660, 2230, 1710, 1455, 1435, 1410, 1315, 1300, 1245, 1130, 1095, 1075, 1020, 970 cm^{-1}; mass spectrum, calcd for $C_{31}H_{57}NO_4Si_3$ [M^+ of tris(trimethylsilyl) derivative], m/e 591.3595; found, m/e 591.3595.

(5*E*)-9β-Cyano-6a-carbaprostaglandin I_2 (19). In a similar manner to the preparation of (5*Z*)-9β-Cyano-6a-carba-PGI_2, methyl ester (**17**) from alcohol **15**, 0.50 g (0.94 mmol) of alcohol **16** was converted to 0.26 g (71%) of (5*E*)-9β-cyano-6a-carba-PGI_2, methyl ester: R_f 0.25 (in 20% hexane in ethyl acetate); NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.08–3.15 (m, 22 H), 3.25–4.6 (m including 3 H singlet at δ 3.67, 7 H), 5.1–5.8 (m, 3 H); IR (film) 3400, 2230, 1740, 1675, 1435, 1315, 1250, 1230, 1200, 1170, 1135, 1095, 1020, 970, 915, 890 cm^{-1}; mass spectrum, calcd for $C_{29}H_{51}NO_4Si_2$ [M^+ of bis(trimethylsilyl) derivative], m/e 533.3356; found, m/e 533.3362. Anal. Calcd for $C_{23}H_{35}O_4N$: C, 70.92; H, 9.06; N, 3.60. Found: C, 70.74; H, 9.01; N, 3.22.

In a similar manner to the preparation of (5*Z*)-9β-cyano-6a-carba-PGI_2 (**18**) from ester **17**, 235 mg (0.60 mmol) of (5*E*)-92-cyano-6a-carba-PGI_2 methyl ester was converted to 217 mg (96%) of acid **19** as a colorless oil: R_f 0.31; NMR δ 0.91 (t, J = 5 Hz, 3 H), 1.06–3.2 (m, 22 H), 3.6–4.4 (m, 2 H), 5.12–5.8 (m, 3 H), 6.27 (br s, 3 H); IR (film) 3380, 2660, 2230, 1735, 1710, 1455, 1435, 1410, 1300, 1245, 1170, 1130, 1095, 1025, 970 cm^{-1}; mass spectrum, calcd for $C_{31}H_{57}O_4NSi_3$ [M^+ of tris(trimethylsilyl) derivative], m/e 591.3595; found, m/e 591.3607.

2-Decarboxy-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-6a,9-didehydro-6a-carbaprostaglandin I_2 11,15-Bis(tetrahydropyranyl) Ether (20). A solution of 4.1 mmol of lithium diisopropylamide (prepared from 0.58 mL (4.1 mmol) of diisopropylamine and 2.6 mL (4.1 mmol) of 1.56 M *n*-butyllithium (in hexane) in 20 mL of THF) at 0 °C was treated with 0.50 g (2.03 mmol) of 6-((*tert*-butyldimethylsilyl)oxy)hexanoic acid (**11**) in 5 mL of THF, stirred for 15 min at 0 °C and 1 h at room temperature, cooled to 0 °C, and treated with 0.88 g (2.03 mmol) of enone **2** in 5 mL of THF. The resulting suspension was allowed to warm to room temperature and after 16 h was acidified and extracted with ether. The ether extracts were washed with brine and dried (Na_2SO_4). The solvents were removed under reduced pressure to give 1.37 g of an oil which was dissolved in 16 mL of methylene chloride and then treated with 2.9 mL (10.4 mmol) of dimethylformamide dineopentyl acetal. The resulting solution was stirred for 3 h at room temperature and then partitioned between 4:1 water–brine and ether. The ether extracts were washed with saturated aqueous sodium bicarbonate and brine and were dried (Na_2SO_4). The solvents were removed under reduced pressure and the residue was chromatographed on silica gel eluted with 10% ethyl acetate in hexane to give 0.75 g (60%) of **20** as a colorless oil: R_f 0.27 and 0.24 (in 10% ethyl acetate in hexane); NMR δ 0.05 (s, 6 H), 0.91 (s, 12 H), 1.1–3.1 (m, 32 H), 3.3–4.5 (m, 8 H), 4.73 (s, 2 H), 4.9–6.17 (m, 4 H); IR (film) 1460, 1250, 1200, 1020, 970, 840 cm^{-1}; mass spectrum, m/e 515, 514, 430, 373, 298, 85.

(5*Z*)-2-Decarboxy-2-(hydroxymethyl)-6a,9-didehydro-6a-carbaprostaglandin I_2 11,15-Bis(tetrahydropyranyl) Ether (21) and (5*E*)-2-Decarboxy-2-(hydroxymethyl)-6a,9-didehydro-6a-carbaprostaglandin I_2 11,15-Bis(tetrahydropyranyl) Ether (22). A solution of 0.71 g (1.15 mmol) of silyl ether **20** in 16 mL of THF at 0 °C was treated with 3.2 mL (2.4 mmol) of 0.75 M tetra-*n*-butylammonium fluoride in THF. The resulting solution was allowed to slowly warm to room temperature and after 16 h partitioned between brine and ethyl acetate. The combined ethyl acetate extracts were washed with 0.5 M aqueous potassium bisulfate, saturated aqueous sodium bicarbonate, and brine and dried (Na_2SO_4). The solvents were removed under reduced pressure to give 0.61 g of an oil which was chromatographed on HPLC silica gel eluted with 35% ethyl acetate in hexane to give 0.30 g (52%) of alcohol **21** (R_f 0.23 in 35% ethyl acetate in hexane) and 0.175 g (30%) of alcohol **22** (R_f 0.29 in 35% ethyl acetate in hexane). Both **21** and **22** are pale yellow oils which rapidly darken upon storage.

21: NMR δ 0.89 (t, J = 5 Hz, 3 H), 1.07–3.1 (m, 33 H), 3.2–4.5 (m, 8 H), 4.72 (br s, 2 H), 4.85–5.85 (m, 3 H), 6.01 (br s, 1 H); IR (film) 3440, 1670, 1655, 1635, 1200, 1130, 1115, 1075, 1035, 1020, 975 cm^{-1}; mass spectrum, m/e 400, 332, 316, 298, 85.

22: NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.07–3.23 (m, 33 H), 3.23–4.55 (m, 8 H), 4.73 (br s, 2 H), 4.93–6.0 (m, 4 H); IR (film) 3440, 1670, 1635, 1200, 1130, 1115, 1075, 1035, 1020, 975, 870 cm^{-1}; mass spectrum, m/e 400, 332, 316, 298, 85.

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Thermal Electrocyclic Reactions of 2-Aza-1,3-butadiene Derivatives. A New N-Heterocyclic Annelation[1]

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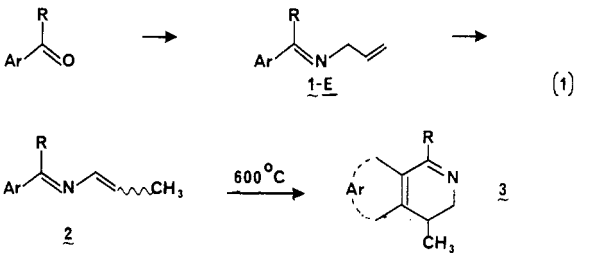
A general, three-step annelation sequence, which ultimately gives 3,4-dihydro-2-quinolines and related derivatives (**3**), is described. The cyclization step is accomplished by pyrolysis of a 1-arenyl-2-aza-1,3-butadiene analogue (**2**) that apparently undergoes successive six-π-electron electrocyclization and 1,5-hydrogen migration reactions to yield the product. The conjugated azadienes, **2**, are prepared by the base-catalyzed isomerization of the unconjugated isomers, **1**. Compounds **1** are prepared by condensing arenyl ketones or aldehydes with 2-propenyl-1-amine. Steric effects of substituents on the azadiene chain and steric and electronic effects of the arenyl group on the cyclization step were studied. The following general conclusions were drawn: alkyl substituents R on the C=N terminus of **2** hinder a competing degradative process (commencing with a four-π-electron electrocyclization) and improve the yield of products **3**; electron-withdrawing substituents on Ar of **2** or electron-withdrawing Ar groups enhance the yield of cyclized products, but they impart little regioselectivity to the reaction; regioselectivity may be imparted by π bond fixation in Ar; electrocyclization also proceeds well with π-electron excessive Ar groups on **2**. The preferred conformation of the heterocyclic product **3** can be readily deduced by ^1H NMR spectroscopy.

Isoquinoline and dihydroisoquinoline ring systems have attracted much attention from chemists because of the spectrum of biological activity they possess.[2,3] Syntheses of the ring systems have relied very heavily on some type of intramolecular electrophilic substitution of a benzene or substituted benzene ring for ring closure. The classical Bischler–Napieralski reaction and the related Pictet–Gams, Pictet–Spengler, and Pomerantz–Fritsch reactions illustrate the approach.[4] This approach has not worked well when electron-withdrawing substituents are present on the benzene (or other aromatic) ring. Also, the approach has not been widely applied to annelations of heterocyclic aromatic rings, such as pyridine. Accordingly, new syntheses of the isoquinoline and di-and tetrahydroisoquinoline ring systems continue to be reported.[4c,5]

Herein we report an annelation based on the thermal electrocyclization of 1-aryl-2-aza-1,3-pentadiene derivatives, **2**, that yields, as initial products, 3,4-dihydroisoquinolines or analogous ring systems **3**. The three-step sequence of eq (1) has proved to be a general one, and works well when Ar is either electronegative or π-electron excessive relative to C_6H_5.



Related Electrocyclizations. About the time this work commenced Bergman and Wendling[6] reported that the thermal decomposition of 2*H*-azirines produced, in part, 2-azabutadienes which, at higher temperatures underwent cyclization to 3,4-dihydroisoquinolines (eq 2). Previously, Weber and co-workers[7] had reported the synthesis of 1,2-dihydronaphthalenes by the gas phase pyrolysis of substituted 1-phenyl-1,3-butadienes. The thermal electrocyclizations of eq (3)[8] and (4)[9] and other examples have been reported.

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