Synthesis of Six-Membered-Ring Analogues of 6α-Carba-PGI_2

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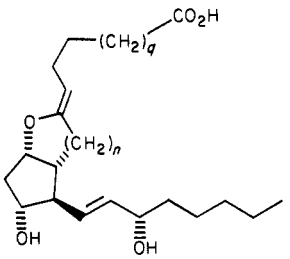
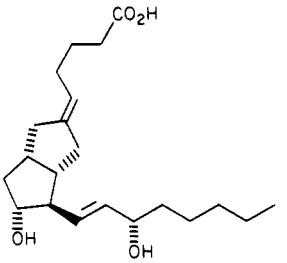
Received April 27, 1982

To further develop our understanding of prostacyclin (PGI_2, 1) structure–activity relationships, we have prepared the six-membered-ring analogues of 6α-Carba-PGI_2 (carbacyclin, 3). An intramolecular alkylation of 1,3-dithiane was utilized as the critical reaction for securing the key cyclohexanone intermediate 8. The carboxyl side chains were attached to 8 by using conventional Wittig chemistry. Acid removal of the tetrahydropyranyl protective groups and separation of the resulting *E* and *Z* isomers afforded the 7a-homo-6α-Carba-PGI_2 analogues 6 and 7. The reactions described are simple to perform and useful for preparative purposes. The six-membered-ring carbacyclins reported were found to be much less active than parent carbacyclin in inhibiting human platelet aggregation.

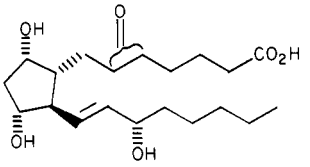
Prostacyclin (PGI_2, 1) is the most potent inhibitor of human platelet aggregation yet discovered and a powerful vasodilator.[1] It is becoming increasingly evident that PGI_2 production by the blood vessel wall plays a significant role in controlling the health and disease of the cardiovascular system.[2] Despite its important biological profile, the potential therapeutic value of PGI_2 is limited by its chemical instability. The rate of hydrolysis to 6-oxo-$PGF_{1\alpha}$ (4) at pH 7.6 is such that the half-life of PGI_2 is about 10



1, $n = 1; q = 1$
2, $n = 2; q = 0$



3



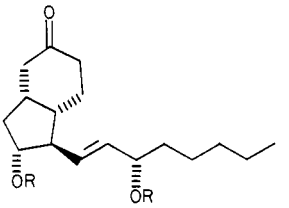
4, 6-oxo
5, 5-oxo

min at 25 °C.[3] Consequently, considerable effort has been expended in attempts to prepare chemically modified analogues of PGI_2.

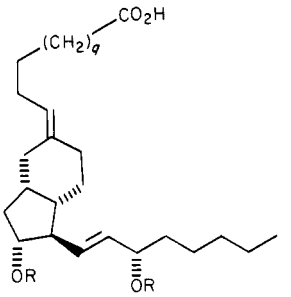
A synthesis of 7a-homo-2-nor-PGI_2 (2) has been described by Johnson[4] where the tetrahydrofuran ring of PGI_2 was replaced with a tetrahydropyran ring. Interestingly, 2 was found to be equipotent in vitro to PGI_2 as an inhibitor of human platelet aggregation.[5] However, 2 inherits the instability of PGI_2 by virtue of its enol ether functionality and rapid hydrolysis to 5-oxo-$PGF_{1\alpha}$ (5). Several groups[6] have now independently reported the synthesis of 6α-Carba-PGI_2 (carbacyclin, 3), a chemically stable analogue possessing desirable pharmacological properties[7] similar to those of natural PGI_2. These important developments dictated the preparation of the six-membered-ring carbacyclin analogue. We report herein a straightforward synthesis of 6 and 7 and some preliminary biological activities.

Results and Discussion

The strategy for the synthesis of 6 or 7 required the preparation of ketone 8 as the key intermediate. Reaction



8, R = THP
9, R = H



6 (4*Z*), R = H; q = 0; 6a (4*E*)
7 (5*Z*), R = H; q = 1; 7a (5*E*)
10 (*E* and *Z* mixture), R = THP; $q = 0$
11 (*E* and *Z* mixture), R = THP; $q = 1$

of 8 with an appropriate Wittig reagent, acid removal of the C-11 and C-15 tetrahydropyranyl (THP) protective groups, and separation of the resulting *Z* and *E* geometric isomers would then afford the six-membered-ring analogues 6 and 7.

(1) (a) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *Nature (London)*, **263**, 663 (1976); (b) R. Gryglewski, S. Bunting, S. Moncada, R. J. Flower, and J. R. Vane, *Prostaglandins*, **12**, 685 (1976); (c) S. Moncada, R. Gryglewski, S. Bunting, and J. R. Vane, *ibid.*, **12**, 715 (1976); (d) S. Bunting, R. Gryglewski, S. Moncada, and J. R. Vane, *ibid.*, **12**, 897 (1976).

(2) (a) S. Moncada, A. G. Herman, E. A. Higgs, and J. R. Vane, *Thromb. Res.*, 11, 323 (1977), and references cited therein; (b) S. Moncada and J. R. Vane, *J. Med. Chem.*, **23**, 591 (1980).

(3) R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Sun, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, **12**, 915 (1976).

(4) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **45**, 3802 (1980).

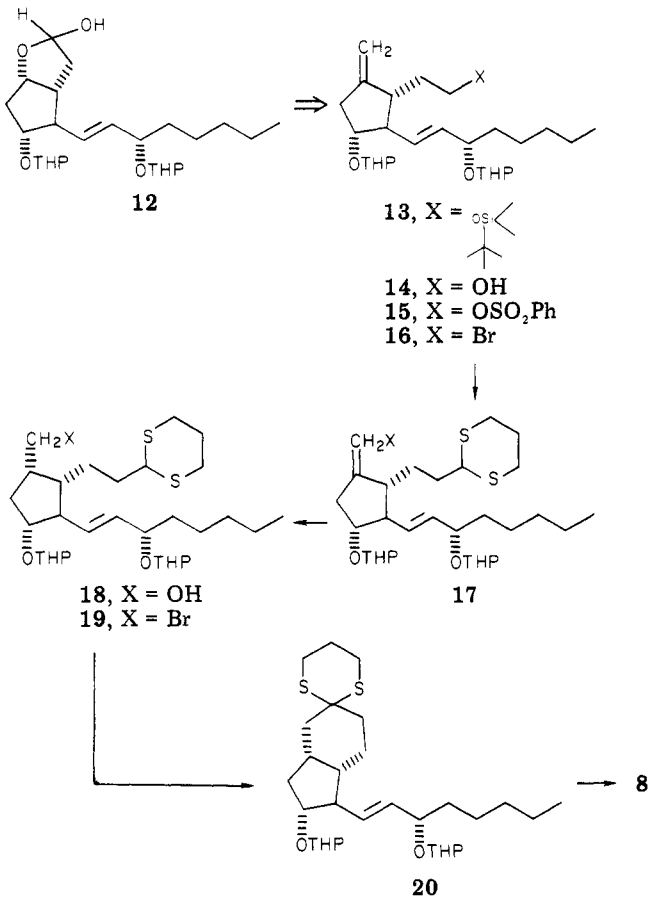
(5) R. A. Johnson and E. G. Nidy, "Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids", S. M. Roberts and F. Scheinmann, Eds., Pergammon Press, London, 1979, pp 274–285.

(6) (a) D. R. Morton and F. C. Brokaw, *J. Org. Chem.*, **44**, 2880 (1979); (b) P. A. Aristoff, *ibid.*, **46**, 1954 (1981); (c) K. C. Nicolaou, W. J. Sipio, R. L. Magolda, S. Seitz, W. E. Barnette, *J. Chem. Soc., Chem. Commun.*, 1067 (1978); (d) K. Kojima and K. Sakai, *Tetrahedron Lett.*, 3743 (1978). (e) H. Nakai, Y. Arai, N. Hamanaka, M. Hayashi, *ibid.*, 805 (1979); (f) C. Gandolfi, Oral Communication at the Symposium on Chemistry and Biochemistry of Prostanoids, Salford, England, July 1978; *Chem. Br.*, **15**, 86 (1979).

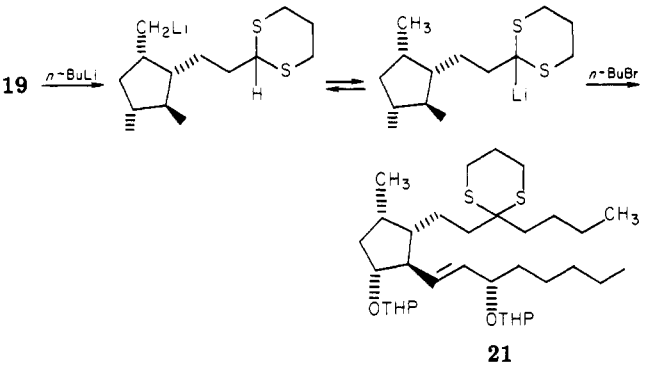
(7) D. R. Morton, G. L. Bundy, and E. E. Nishizawa in "Prostacyclin", J. R. Vane and S. Bergstrom, Eds., Raven Press, New York, 1979, pp 31–41.

0022-3263/82/1947-4311$01.25/0

Scheme I



Scheme II



The preparation of 8 (Scheme I) was accomplished starting with silyl ether **13**, a readily available PG intermediate commonly employed in our laboratory for PG analogue synthesis. Experimental details for the preparation of **13** from chiral lactol **12**[8] are provided in the Experimental Section.

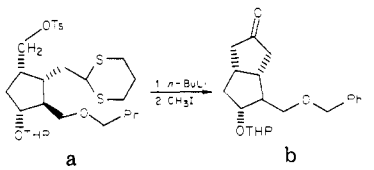
Transformation of **13** to bromide **16** was readily achieved in 90% overall yield by (a) desilylation of **13** to alcohol **14** with tetra-*n*-butylammonium fluoride,[9] (b) conversion of **14** to benzenesulfonate **15**, and (c) treatment of **15** with lithium bromide in DMF to produce **16**. The thioacetal **17** was prepared in 95% yield by addition of **16** to a −20 °C tetrahydrofuran solution of 2-lithio-1,3-dithiane. Hydroboration of **17** with 9-borobicyclo[3.3.2]nonane (9-BBN) and careful oxidative workup yielded alcohol **18**.[10] The bromide **19** was then obtained from alcohol **18** (88% yield from 18) in the same manner as previously described for the preparation of **16** from 14. Treatment **19** with lithum diisopropylamide in tetrahydrofuran (1.3 equiv, −20 °C, 3 h) afforded thioketal **20**[11] in quantitative yield. When *n*-butyllithium was used as the base, halogen–metal exchange occurred, resulting in the formation of some 9-methyl thioketal **21** (Scheme II).

Several different methods [$Ce(NH_4)_2(NO_3)_6$,[12] $HgCl_2$–$CaCO_3$,[13] $CuCl_2$–CuO[14]] were tried for unmasking the carbonyl group of **20**. These reactions gave complex mixtures of polar products arising from cleavage of the THP blocking groups. The use of methyl iodide[15] (20 equiv) and $CaCo_3$ (3 equiv) in acetonitrile–water (5:1, 40 °C, 17 h) proved superior and afforded ketone **8**[16] in 70% yield.

The attachment of the carboxylic acid side chain to **8** was achieved under standard Wittig reaction conditions. Thus, reaction of **8** with (3-carboxy-*n*-propyl)triphenylphosphorane provided acid **10**; correspondingly, reaction with (4-carboxy-*n*-butyl)triphenylphosphorane furnished acid **11**. Acid removal of the C-11 and C-15 THP protective groups from **10** and **11** afforded acids **6** and **6a** and acids **7** and **7a**, respectively. At this stage[17] we were fortunate that the *E* and *Z* isomers were easily separated by LPLC. The *E* and *Z* configurational assignments of the final products have not, as yet, been definitively determined. The present assignments are tentative and based on comparison of relative TLC polarities to that of carbacyclin (**3**).[6a] Therefore, in each instance, the more polar isomer has been assigned the *Z* configuration.

The utilization of 1,3-dithianes in intramolecular alkylations[18] provides a high-yielding method for obtaining five- and six-membered cycloalkanone carbacyclin intermediates.[19] The synthesis described here avoids difficult chromatographic separations and, oftentimes, involved a simple gravity filtration through silica gel. In many instances, the crude product (**15–17**, **19**, **20**) was used directly in the synthesis without further purification.

(8) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.* **92**, 397 (1970).
(9) E. J. Corey and A. Venkatesuwarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(10) The 9β-hydroxymethyl epimer was obtained in 5–7% yield.
(11) To achieve a high yield of the inter- and intramolecular alkylation products, 17 and 20, it was imperative to use the bromide derivatives; use of the benzenesulfonate leaving group gave, at best, a low yield of product.
(12) T. L. Ho, H. C. Ho, and C. M. Wong, *J. Chem. Soc., Chem. Commun.*, 791 (1972).
(13) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).
(14) K. Narasaka and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **45**, 3724 (1972).
(15) B. T. Grobel and D. Seebach, *Synthesis*, 357 (1977), and references cited therein.
(16) The 9α,8α ring fusion of **8** was firmly established by comparison with a sample of **8** prepared by P. A. Aristoff using the chemistry described in ref 6b. This route gave both **8** and its 9β,8α ring isomer. TLC analyses of **8** prepared in this study showed the absence of any 9β,8α isomer.
(17) The *E* and *Z* isomers of the corresponding methyl ester derivatives were not separable by conventional silica gel chromatography.
(18) The ring closure of (chloroalkyl)-1,3-dithianes with *n*-BuLi has been reported to give in good yields three-, four-, five-, and six-membered rings. See D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **33**, 300 (1968). However, the use of 1,3-dithianes in intramolecular reactions to form fused [4.3.0] and [3.3.0] rings is not widely documented.
(19) This chemistry has also been successfully applied to tosylate a for the preparation of cyclopentanone b, a common intermediate useful in carbacyclin analogue synthesis.



When tested in vitro against ADP-induced human platelet aggregation, **6a**, **7**, and **7a** were found inactive (ED_{50} > 1000 ng/mL). The 4*Z* analogue **6** possessed very marginal activity (ED_{50} > 500 < 1500 ng/mL). In the same screen, PGI_2 sodium salt is effective at ED_{50} = 1–2 ng/mL and carbacyclin (**3**) at ED_{50} = 20–30 ng/mL. In rat blood pressure experiments, **6**, **6a**, and **7a** were found comparable to PGE_1 in lowering blood pressure while **7** possessed 0.1–0.32% the depressor activity of PGE_1. In light of the high antiaggregatory properties of carbacyclin (**3**) and 7a-homo-2-nor-PGI_2 (**2**), it is surprising that **6** does not exhibit similar activity.[20]

Experimental Section[21]

Preparation of Dimethyl-*tert*-butylsilyl Ether 13. Step 1. To a magnetically stirred suspension of $LiAlH_4$ (5.510 g, 145 mmol) in 350 mL of ether, cooled in an ice–water bath, was added a solution of lactol **12** (21.25 g, 48.52 mmol) in 120 mL of ether. Stirring was maintained at ambient temperature for 22 h. The reaction flask was cooled in an ice bath, and 50 mL of saturated Na_2SO_4 solution was cautiously added dropwise to destroy the excess reagent. The resulting gelatinous aluminum salts were coagulated by addition of solid anhydrous Na_2SO_4 powder and ether (400 mL). The solids were removed by suction filtration through Celite, and the filtrate was concentrated in vacuo to give 20.40 g of a colorless oil. TLC in EtOAc gave R_f 0.29.

Step 2. To a magnetically stirred solution of the product obtained in step 1 (16.65 g, 37.84 mmol) and imidazole (3.602 g, 52.48 mmol) in 80 mL of DMF, cooled in a −78 °C bath, was added dropwise over 12 min a solution of dimethyl-*tert*-butylsilyl chloride (6.264 g, 41.62 mmol) in 50 mL of DMF. After the addition, the resulting solution was stirred at −15 to −10 °C for 2 h. Crushed ice (10–15 g) was added, the contents were stirred for 10 min and diluted with 1 L of ether. The ether solution was washed three times with water and saturated brine and then dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded 20.20 g of crude product. This material was chromatographed with 500 g of silica gel packed with Skellysolve B–EtOAc (2:1). With 40-mL fractions, elution with the same solvent gave 19.44 g of pure product. For TLC in Skellysolve B–EtOAc (2:1): R_f 0.45; ^{1}H NMR (CCl_4) δ 5.40 (m, 2 H), 4.65 (m, 2 H), 4.30–3.10 (m, 11 H), 2.75–1.10 (m, 26 H), 0.88 (s, 12 H), 0.07 (s, 6 H); IR (film) 3470, 2940, 1020, 975, 840, 780 cm^{-1}.

Step 3. Solid CrO_3 (23.30 g, 233 mmol) was added under nitrogen in several portions to a mechanically stirred solution of pyridine (36.81 g, 466 mmol) in 500 mL of CH_2Cl_2 cooled in a 0–5 °C bath. Stirring was continued at room temperature for 1 h. At the end of this period, the flask was placed in a 0–5 °C bath, and a solution of the product obtained from step 2 (18.44 g, 33.29 mmol) in 215 mL of CH_2Cl_2 was added over 14 min. Stirring was then maintained at room temperature for 1 h. After addition of Celite (seven or eight tablespoons), the crude reaction mixture was filtered through a 1-L glass-sintered funnel packed with silica gel–Celite (1:1). The solid cake was washed thoroughly with 1 L of ether. Evaporation of the filtrate in vacuo yielded 17.45 g of product. For TLC in Skellysolve B–EtOAc (2:1): R_f 0.58, 0.54, 0.51 (THP anomers); ^{1}H NMR (CCl_4) δ 5.65 (m, 2 H), 4.70 (m, 2 H), 3.78 (t, 2 H, *J* = 6 Hz), 4.30–3.30 (m, 6 H), 3.00–1.20 (m, 26 H), 0.95 (s, 12 H), 0.08 (s, 6 H); IR (film) 2950, 1740, 975, 840, 780 cm^{-1}.

Step 4. To a magnetically stirred solution of *N*-methyl-*S*-methyl-*S*-phenylsulfoximine (11.92 g, 70.56 mmol) in 100 mL of THF, cooled in a 0–5 °C bath, was added under nitrogen 24 mL (70.56 mmol) of 2.95 M CH_3MgCl. Stirring was continued at 0–5 °C for 15 min. The sulfoximine anion solution was then added under nitrogen to a mechanically stirred solution of the product from step 3 (18.55 g, 33.60 mmol) in 125 mL of THF cooled in a −78 °C acetone–dry ice bath. TLC analysis (4:1 Skellysolve B–EtOAc) after 15 min at −78 °C showed a trace of starting material and predominantly the sulfoxime addition product. The acetone–dry ice bath was replaced with an ice–water bath, and 300 mL of THF, 70 mL of water, 70 mL of acetic acid, and Al(Hg) (prepared from 20 g of Al and 10 g of $HgCl_2$ in 500 mL of water) were added. The reaction mixture was maintained between 20 and 30 °C. TLC analysis after 30 min showed some unreacted sulfoxime adduct. Therefore, an additional amount of Al(Hg), prepared from 7 g of Al, was added and stirring continued at 25 °C for 70 min. At the end of this period, the contents were filtered through Celite by using EtOAc (1 L), and the filtrate was diluted with 700 mL of hexane. The organic solution was successively washed three times with saturated brine, three times with saturated $NaHCO_3$ solution, and with saturated brine. It was then filtered through anhydrous Na_2SO_4. Removal of the solvent in vacuo gave 27.14 g of crude product. This material was chromatographed with 500 g of silica gel packed with Skellysolve B–EtOAc (20:1). With 40-mL fractions, elution with the same solvent yielded 13.86 g of pure **7**: TLC (Skellysolve B–EtOAc, 10:1) R_f 0.25; ^{1}H NMR (CCl_4) δ 5.50 (m, 2 H), 4.88 (m, 2 H), 4.68 (m, 2 H), 3.67 (t, 2 H, *J* = 6 Hz), 4.20–3.20 (m, 6 H), 2.90–1.15 (m, 26 H), 0.90 (s, 12 H), 0.05 (s, 6 H); IR (film) 2995, 1650, 975, 840, 780 cm^{-1}.

Preparation of Alcohol 14. To a magnetically stirred solution of **13** (21.78 g, 39.60 mmol) in 65 mL of THF was added under nitrogen 80 mL of 0.75 M tetra-*n*-butylammonium fluoride. Stirring was continued at ambient temperature for 18 h. The solution was diluted with 1 L of EtOAc and washed with saturated brine, ice-cold 0.5 M $KHSO_4$ solution, 5% $NaHCO_3$ solution, and saturated brine in succession. The EtOAc solution was dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo gave 21.60 g of crude product. This material was chromatographed with 500 g of silica gel packed with Skellysolve B–EtOAc (2:1). With 40-mL fractions, elution with the same solvent yielded 16.65 g (96% yield) of pure **14**: TLC (Skellysolve B–EtOAc, 2:1) R_f 0.33; ^{1}H NMR ($CDCl_3$) δ 5.70–5.35 (m, 2 H), 4.90 (m, 2 H), 4.65 (m, 2 H), 4.20–3.20 (m, 8 H), 2.90–1.10 (m, 27 h), 0.88 (t, 3 H); IR (film) 3450, 1650, 1020, 980 cm^{-1}. Anal. Calcd for $C_{26}H_{44}O_5$: C, 71.62; H, 10.16. Found: C, 71.32; H, 10.33.

Preparation of Benzenesulfonate 15. Alcohol 14 (14.43 g, 33.09 mmol) was placed in 60 mL of pyridine with 7.88 g (44.67 mmol) of benzenesulfonyl chloride and kept at 0–5 °C for 22 h. Crushed ice (5–10 g) was then added. The solution was stirred at 25 °C for 15 min followed by dilution with 600 mL of ether. The ether solution was washed with 5% $NaHCO_3$, two times with ice-cold 2% HCl, 5% $NaHCO_3$, water, and saturated brine in succession and dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded 17.65 g (93% yield) of pure **15**: TLC (Skellysolve B–EtOAc, 4:1) R_f 0.31; ^{1}H NMR ($CDCl_3$) δ 5.50 (m, 2 H), 4.90 (m, 1 H), 4.67 (m, 3 H), 4.13 (t, 2 H, *J* = 6 Hz), 4.10–3.25 (m, 6 H), 2.80–1.10 (m, 26 H), 0.88 (t, 3 H); IR (film) 2950, 1650, 1360, 1180, 970 cm^{-1}.

Preparation of Bromide 16. To a magnetically stirred solution of **15** (17.65 g, 30.64 mmol) in 125 mL of DMF, cooled in a 0–5 °C bath, were added 2.573 g (30.64 mmol) of $NaHCO_3$ and 7.905 g (91.92 mmol) of LiBr. Stirring was continued at 25 °C for 23 h. The reaction mixture was diluted with 700 mL of ether and washed with 200 mL of 5% $NaHCO_3$, three times with water, and with saturated brine, and the ether extract was dried with

(20) During the course of our work, there appeared in the patent literature (Patent GB 2013661A) a claim by Farmitalia Carla Erba that **7** was equipotent to carbacyclin (**3**) in inhibition of ADP-induced human platelet aggregation. **7** prepared in this study was found to be at least 30–50 times less active than **3**.

(21) The ^{1}H NMR spectra were obtained on a Varian A-60D or a Varian HFT-80 spectrometer. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. The ^{1}H NMR spectra of the dimethyl-*tert*-butylsilyl ether derivatives were obtained in carbon tetrachloride without an internal standard. Infrared spectra were recorded with either a Perkin-Elmer Model 137 or 139 or a Digilab Model FTS-14D. High-resolution mass spectra were obtained on the derivatized (Me_3Si) compounds with a CEC 21-110B spectrometer. Column chromatography utilized neutral silica gel (E. Merck, 70–230 mesh). LPLC refers to low-pressure liquid chromatography with E. Merck Lobar silica gel 60 prepacked columns. The sovlents were driven by a Milton-Roy D pump. Acid-washed silica gel was Mallinckrodt CC-4. All TLC analyses were carried out on silica gel GF plates (250 μm, Analtech). The homogeneity of the crude reaction products, that were employed directly in the synthesis without further purification, was based on TLC analyses in two or more different solvent systems. Unless otherwise indicated, the compounds prepared in this study were obtained as viscous oils, and the yields reported were determined after drying to constant weight under high vacuum at 40 °C. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reactions were done under an inert nitrogen atmosphere.

anhydrous Na_2SO_4. Removal of the solvent in vacuo yielded 15.24 g (100% yield) of pure **16**: TLC (Skellysolve B–EtOAc, 7:1) R_f 0.34; ^1H NMR ($CDCl_3$) δ 5.60 (m, 2 H), 4.90 (m, 1 H), 4.83 (m, 1 H), 4.68 (m, 2 H), 3.45 (t, 2 H, J = 7 Hz), 4.20–3.45 (m, 6 H), 2.80–1.10 (m, 26 H), 0.88 (t, 3 H); IR (film) 2950, 1650, 1020, 975 cm^{-1}.

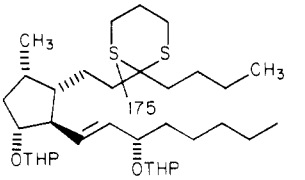
Preparation of Thioacetal 17. *n*-BuLi (1.6 M in hexane, 25 mL, 40 mmol) was added under nitrogen to a magnetically stirred solution of 1,3-dithiane (4.637 g, 38.64 mmol) in 70 mL of THF maintained in a −20 °C constant-temperature bath. Stirring was continued at this temperature for 2 h. At the end of this period, **16** (14.80 g, 29.72 mmol) was added over 3.5 min and the reaction mixture kept at −20 °C for an additional 2.5 h. The pale yellow solution was then poured into 150 mL of ice–water and extracted with ether. The ether solution was washed with water, 5% $NaHCO_3$, and saturated brine and then dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo furnished 16.94 g of **17**. TLC (Skellysolve B–EtOAc, 10:1; two passes) for **16** gave R_f 0.32, 0.27 (THP anomers). For **17**: TLC (as for **16**) R_f 0.25, 0.22 (THP anomers); ^1H NMR ($CDCl_3$) δ 5.55 (m, 2 H), 4.85 (m, 2 H), 4.68 (m, 2 H), 4.20–3.20 (m, 7 H), 3.00–1.10 (m, 34 H), 0.88 (t, 3 H); IR (film) 2990, 1650, 1020, 975 cm^{-1}. The crude product was used without further purification.

Preparation of Alcohol 18. To a magnetically stirred solution of **17** (14.65 g, 27.23 mmol) in 80 mL of THF, cooled in a 0–5 °C bath, was added under nitrogen 140 mL (70.0 mmol) of 0.5 M 9-BBN. Stirring was continued at 0–5 °C for 3.5 h. At the end of this period, 12 mL of water was added. After the reaction solution was stirred for 2 min, 25 mL of 3 N NaOH and 16 mL of 30% H_2O_2 were added simultaneously over a 3-min period. The reaction flask was cooled intermittently in a water bath to maintain the solution temperature at 25 °C, and stirring was continued for 15 min. The reaction mixture was then diluted with 250 mL of saturated brine and extracted two times with ether. The ether–THF extract was concentrated in vacuo, and the residual oil was picked up with 500 mL of ether, washed three times with water and with saturated brine, and dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo gave 16.95 g of crude product. This material was chromatographed with 500 g of silica gel packed with Skellysolve B–EtOAc (1:1). With 40 mL fractions, elution with the same solvent afforded 11.66 g (fractions 40–56) of pure **18**: TLC (EtOAc–Skellysolve B, 1:1) R_f 0.25; ^1H NMR ($CDCl_3$) δ 5.55 (m, 2 H), 4.69 (m, 2 H), 4.17–3.17 (m, 10 H), 3.00–2.67 (m, 4 H), 2.50–1.10 (m, 19 H), 0.88 (t, 3 H); IR (film) 3450, 1020, 975, 900, 730 cm^{-1}. Anal. Calcd for $C_{30}H_{52}O_5S_2$: C, 64.71; H, 9.41; S, 11.52. Found: C, 65.01; H, 9.48; S, 11.82. Fractions 57–72 contained a 1:1 mixture of **18** and a slightly more polar product. The spectral properties of this mixture were nearly identical with those of pure **18**. We have assigned this more polar product to the 9β-hydroxymethyl epimer.

Preparation of Bromide 19. By use of the same procedure described for the preparation of **15**, 11.66 (20.97 mmol) of **18**, 50 mL of pyridine, and 6.66 g (37.75 mmol) of benzenesulfonyl chloride gave 13.78 g of the benzenesulfonate derivative of **18**: TLC (Skellysolve B–EtOAc, 2:1) R_f 0.42, 0.38 (THP anomers); ^1H NMR ($CDCl_3$) δ 7.90 (m, 2 h), 7.60 (m, 3 H), 5.40 (m, 2 H), 4.6 (m, 2 H), 4.20–3.10 (m, 9 H), 2.81 (m, 4 H), 2.60–1.10 (m, 35 H), 0.88 (t, 3 H); IR (film) 2900, 1450, 1350, 1180, 975, 730 cm^{-1}. The crude sulfonate (19.80 mmol) was placed in a mixture of 100 mL of DMF, 6.88 g (80 mmol) of LiBr, and 1.68 g (20 mmol) of $NaHCO_3$, and the mixture was warmed under nitrogen in a 40 °C oil bath. TLC analysis at 14 h showed approximately 10% unreacted starting material; therefore, 0.750 g of LiBr was added, and the reaction was allowed to proceed an additional 10 h at 40 °C. The reaction mixture was worked up in the same manner as previously described for bromide **16** to give 12.00 g of **19**: TLC (Skellysolve B–EtOAc, 3:1) R_f 0.52; ^1H NMR ($CDCl_3$) δ 5.55 (m, 2 H), 4.65 (m, 2 H), 4.22–3.65 (m, 5 H), 3.60–3.10 (m, 4 H), 2.85 (m, 4 H), 2.65–1.10 (m, 35 H), 0.88 (t, 3 H); IR (neat) 2900, 1020, 975, 730 cm^{-1}. The crude product was used without further purification.

Preparation of Thioketal 20. To a magnetically stirred solution of diisopropylamine (2.35 g, 23.28 mmol) in 60 mL of THF, cooled in a −78 °C bath, was added under nitrogen 13.75 mL (22.00 mmol) of 1.6 M *n*-BuLi. Stirring was continued at −78 °C for 20 min. A solution of bromide **19** (10.58 g, 17.12 mmol) was then added to the −78 °C solution of lithium diisopropylamide over a 3.5-min period. After addition, the reaction solution was placed in a −20 to −22 °C constant-temperature bath for 3 h. The contents were then poured into 200 mL of ice–water and extracted two times with ether (1 L). The ether extract was washed with water and saturated brine and then dried with anhydrous Na_2SO_4. Removal of the solvent in vacuo afforded 9.20 g of **20**: TLC (Skellysolve B–EtOAc, 5:1) R_f 0.31 (major), 0.30, 0.26 (minor), resulting from separation of THP anomers; ^1H NMR ($CDCl_3$) δ 5.45 (m, 2 H), 4.68 (m, 2 H), 4.27–3.15 (m, 6 H), 3.10–1.10 (m, 37 H), 0.88 (t, 3 H); IR (film) 2990, 1430, 1195, 1010, 975, 860 cm^{-1}; mass spectrum, m/e 538 (M^+, weak); calcd for $C_{25}H_{41}O_3S_2$ (M^+ − 85) m/e 453.2497, found 453.2496. The crude product was used without further purification.

In another experiment, 0.490 g (0.80 mmol) of **19** in 5 mL of THF was treated with 0.52 mL (0.84 mmol) of 1.6 M *n*-BuLi (5 h, −20 °C). The reaction mixture was worked up as described above to give 0.405 g of crude product. The major component was isolated after LPLC by using Skellysolve B–EtOAc (9:1) and identified as ketal **21**: ^1H NMR ($CDCl_3$) δ 5.45 (m, 2 H), 4.68 (m, 2 H), 4.15–3.15 (m, 6 H), 2.80 (m, 4 H), 2.65–1.15 (m, 37 H), 1.05–0.85 (m, 9 H); mass spectrum calcd for $C_{29}H_{50}O_2S_2$ (M^+ − THPOH), m/e 494.3252, found 494.3249; calcd for $C_8H_{15}S_2$ (see below) m/e 175.0615, found 175.0620.



Preparation of Cyclohexanones 8 and 9. Thiaketal **20** (7.10 g, 13.19 mmol) was placed in 220 mL of CH_3CN, 40 mL of water, 3.96 g (39.57 mmol) of $CaCO_3$, and 18 mL of methyl iodide, and the mixture was warmed in a 40 °C oil bath for 17 h. After cooling to room temperature, the reaction mixture was diluted with 750 mL of ether and washed two times with 10% $Na_2S_2O_3$ (300 mL), water, and saturated brine. The aqueous washings were extracted with 500 mL of EtOAc. The combined extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo to give 5.865 g of crude product. This material was chromatographed with 210 g of silica gel packed with Skellysolve B–EtOAc (2:1). Elution with the same solvent afforded 4.130 g of **8**; elution with EtOAc–Skellysolve B (2:1) yielded 0.378 g of a monotetrahydropyranyl derivative which was subjected to pyranylation conditions (dihydropyran, pyridine hydrochloride in CH_2Cl_2, 25 °C, 15 h) to give an additional 0.455 g of **8**: TLC (EtOAc) R_f 0.69; ^1H NMR ($CDCl_3$) δ 5.50 (m, 2 H), 4.66 (m, 2 H), 4.09 (m, 4 H), 3.50 (m, 2 H), 2.50–0.95 (m, 31 H), 0.88 (t, 3 H); IR (film) 2990, 1710, 1020, 980, 860 cm^{-1}. Anal. Calcd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 71.90; H, 10.01.

A sample of **8** (100 mg) was treated with 10 mL of HOAc–H_2O–THF (20:10:3) at 45 °C for 2 h. The solvents were removed in vacuo, and the resulting oil was chromatographed by LPLC. Elution with EtOAc–MeOH (25:1) gave 50 mg of **9**: TLC (EtOAc) R_f 0.16; ^1H NMR ($CDCl_3$) δ 5.55 (m, 2 H), 4.03 (m, 2 H), 2.75–1.10 (m, 21 H), 0.88 (t, 3 H); IR (film) 3550, 2990, 1710, 970 cm^{-1}; mass spectrum (Me_3Si derivative), m/e 424 (M^+); calcd for $C_{23}H_{44}O_3Si_2$ m/e 424.2829, found 424.2811.

Preparation of 7a-Homo-6α-carba-PGI$_2$ Analogues 6, 6a, 7 and 7a. Sodium hydride (60% oil dispersion; 0.287 g, 7.16 mmol; washed two times with hexane) was placed in 12 mL of Me_2SO and heated under nitrogen for 1 h in a 68–72 °C oil bath. The greenish gray solution was allowed to cool to room temperature, and then 1.532 g (3.58 mmol) of (3-carboxy-*n*-propyl)triphenylphosphonium bromide was added under nitrogen in several portions. Stirring a continued at 25 °C for 20 min. At the end of this time, a solution of **8** (0.500 g, 1.12 mmol) in 8 mL of Me_2SO was added dropwise over 3.5 min, and the reaction mixture was allowed to stir for 2 h at 25 °C. The contents were then diluted with 100 mL of ice–water and extracted with ether (75 mL), and the aqueous solution was acidified to pH 5 with 2 N $KHSO_4$ solution. The aqueous solution was extracted with ether (2 × 300 mL), and the combined ether extracts were washed with saturated brine and dried with anhydrous Na_2SO_4. Removal of the solvent

in vacuo gave an oil which was chromatographed with 150 g of acid-washed CC-4 silica gel. Elution with hexane–EtOAc (3:1) gave 0.464 g of **10**, TLC (hexane–EtOAc, 4:1, containing 1% HOAc) R_f 0.28. A portion of **10** (0.291 g, 0.56 mmol) was hydrolyzed with stirring in 12 mL of HOAc–H_2O–THF (20:10:3) at 45 °C for 2 h. The solvents were removed in vacuo to afford 0.253 g of crude product. This material as chromatographed by LPLC (two Lobar B columns connected in series) with $CHCl_3$–MeOH–HOAc (1000:50:5) to yield 0.058 g of **6a** (4*E* isomer) and 0.108 g of **6** (4*Z* isomer), both as viscous colorless oils. TLC in $CHCl_3$–MeOH–HOAc (15:1:0.15) gave R_f 0.31 for **6a** and R_f 0.24 for **6**: ^{1}H NMR ($CDCl_3$; the spectra of **6a** and **6** were very similar) δ 5.70 (br s, OH's), 5.51 (m, 2 H), 5.17 (m, 1 H), 4.30–3.50 (m, 2 H), 2.75–1.10 (m, 23 H), 0.88 (t, 3 H); IR (film; the spectra of **6a** and **6** were identical) 3300–2800 (br, s), 1705, 1120, 975 cm^{-1}; mass spectrum (Me_3Si derivative), *m/e* 566 (M^+); calcd for $C_{30}H_{58}O_4Si_3$ *m/e* 566.3643, found 566.3622 (**6a**), 566.3639 (**6**).

By use of the exact same procedure as described above, reaction of **8** with (4-carboxy-*n*-butyl)triphenylphosphonium bromide gave **7a** (5*E* isomer) and **7** (5*Z* isomer). TLC in $CHCl_3$–MeOH–HOAc (9:1:0.2) gave R_f 0.52 for **7a** and R_f 0.49 or **7**: ^{1}H NMR ($CDCl_3$) for **7a** δ 6.62 (br s, OH's), 5.47 (m, 2 H), 5.10 (m, 1 H), 4.25–3.50 (m, 2 H), 2.80 (m, 25 H), 0.88 (t, 3 H); for **7** δ 6.85 (br s, OH's), 5.50 (m, 2 H), 5.12 (m, 1 H), 4.20–3.60 (m, 2 H), 2.75–1.10 (m, 25 H), 0.88 (t, 3 H); IR (film; the spectra of **7a** and **7** were identical) 3300–2800 (br, s), 1705, 1120, 970 cm^{-1}; mass spectrum (Me_3Si derivative), *m/e* 570 (M^+, weak); calcd for $C_{30}H_{57}O_4Si_3$ ($M^+ - CH_3$) *m/e* 565.3364, found 565.3550 (**7a**), 565.3552 (**7**).

Registry No. **6**, 82933-66-2; **6** TMS, 82933-67-3; **6a**, 82977-35-3; **6a** TMS, 82977-36-4; **7**, 71934-99-1; **7** TMS, 82933-68-4; **7a**, 71963-53-6; **7a** TMS, 82977-37-5; **8**, 82933-69-5; **9**, 82933-70-8; **9** TMS, 82933-71-9; (*E*)-**10**, 82933-72-0; (*Z*)-**10**, 82977-38-6; (*E*)-**11**, 82933-73-1; (*Z*)-**11**, 82977-39-7; **12**, 37435-65-7; **13**, 82933-74-2; **14**, 82933-75-3; **15**, 82933-76-4; **16**, 82933-77-5; **17**, 82951-10-8; **18**, 82933-78-6; **18** (9β epimer), 82977-40-0; **18** benzenesulfonate, 82933-79-7; **19**, 82951-11-9; **20**, 82933-80-0; **21**, 82933-81-1; (3-carboxypropyl)triphenylphosphonium bromide, 17857-14-6; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.

Regioselective Addition of Grignard Reagents to 1-Acylpyridinium Salts. A Convenient Method for the Synthesis of 4-Alkyl(aryl)pyridines

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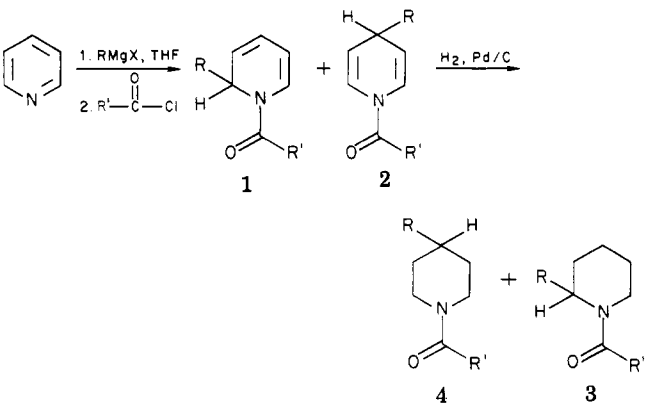
Received April 22, 1982

The addition of Grignard reagents to 1-acylpyridinium salts afforded 1-acyl-2-alkyl(aryl)-1,2-dihydropyridines and 1-acyl-4-alkyl(aryl)-1,4-dihydropyridines. The regioselectivity of this reaction, 1,2- vs. 1,4-addition, was examined and found to be dependent upon the structures of the Grignard reagent and the 1-acyl group. Pyridine, 2-picoline, and 3-picoline were studied, and in most cases, significant amounts of 1,4-addition occurred. When a catalytic amount of cuprous iodide was present, nearly exclusive 1,4-addition resulted. The crude 1,4-dihydropyridines were aromatized by heating with sulfur to provide 4-substituted pyridines and picolines in good yield and high isomeric purity.

The synthesis of substituted pyridines by the reaction of Grignard reagents and pyridine is not a practical method due to the strenuous conditions required for addition, the low yields obtained, and frequent lack of regioselectivity.[1] To obtain high yields of addition with Grignard reagents, activation of the pyridine ring is necessary. Fraenkel and co-workers[2] reported that the pyridine ring could be readily attacked by Grignard reagents in the presence of ethyl chloroformate to provide 2-substituted 1-(ethoxycarbonyl)-1,2-dihydropyridines. Lyle and co-workers[3] elaborated on this method by demonstrating that acid chlorides (e.g., acetyl chloride and benzoyl chloride) are also effective in activating the pyridine ring toward attack by Grignard and organocadmium reagents. The intermediate 1,2-dihydropyridines can be readily oxidized by heating with sulfur to provide 2-substituted pyridines in good yield.[4] The reaction of Grignard reagents with 1-acylpyridinium salts appeared from examination of the literature to form preferentially 1,2-dihydropyridines by attack at the 2-position of the pyridine ring. However, the degree of regioselectivity was unclear since 4-alkylpyridines, in which the 4-position is blocked, were used as starting material in most of the reactions studied thus far.[2-4] It was therefore of interest to study the regioselectivity of this reaction with regard to how the structures of the acyl halide and Grignard reagent influence the de-

Scheme I



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