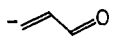
(6) Various procedures for anion formulated as i have been devised: E. J. Corey,



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B. W. Erickson, and R. Noyori, *J. Am. Chem. Soc.*, **93**, 1724 (1971); T. Nakai, H. Shiono, and M. Okawara, *Tetrahedron Lett.*, 3625 (1974); Y. Leroux and C. Roman, *ibid.*, 2585 (1973); T. Cohen, D. A. Bennett, and A. J. Mura, Jr., *J. Org. Chem.*, **41**, 2506 (1976); P. T. Lansbury and R. W. Britt, *J. Am. Chem. Soc.*, **98**, 4578 (1976); M. Wada, H. Nakamura, T. Taguchi, and H. Takei, *Chem. Lett.*, 345 (1977); see also E. J. Corey, C. U. Kim, R. H. K. Chen, and M. Takeda, *J. Am. Chem. Soc.*, **94**, 4395 (1972), and ref 5b.

(7) (a) Cyclopropanols react with proton and halogenating agents.[2] (b) An attempt to effect a fluoride catalyzed reaction of **5** failed; cf. R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **99**, 1265 (1977).

(8) K. Rühlmann, *Synthesis*, 236 (1971).

(9) (a) Preparation of 4-hydroxyheptanoic lactone illustrates the standard reaction conditions. A solution of **5** (6.09 g, 35 mmol) in 10 mL of methylene chloride was added during 5 min to a thick yellow suspension of $TiCl_4$ (6.26 g, 33 mmol) and propanal (2.16 g, 30 mmol) in 20 mL of methylene chloride at −78 °C under nitrogen. The resulting dark brown solution was stirred for 15 min at −78 °C, and for 1 h at 0 °C, and quenched by slow addition of water. The crude product consisted mainly of the expected lactone. Treatment of the crude lactone with *p*-toluenesulfonic acid hydrate in refluxing benzene gave, on distillation, 2.96 g (77%) of the lactone, bp 76–78 °C (2.3 mm). (b) All final compounds in the text were fully characterized by spectral data and elemental composition. All yields referred to are isolated (TLC or distillation) yields.

(10) Distilled product showed two methyl doublets of equal intensities at δ 1.57 (J = 7 Hz) and at δ 1.74 (J = 5 Hz) on NMR. IR spectrum exhibited only a trans olefinic bond at 967 cm^{-1} of medium intensity.

(11) (a) BF_3·Et_2O, $AlCl_3$, Cp_2TiCl_2, and $ZrCl_4$ brought about only very slow consumption of starting materials and/or gave complex mixture. $SnCl_4$ reacted with **5**, even in the presence of an acetal to give a β-stannyl ester in good yield. (b) We have not yet been successful to effect the coupling of **5** with aliphatic acetals and benzoyl chloride. This observation strongly contrasts with the high reactivities of enol silyl ethers with these substrates (T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974); E. Nakamura and I. Kuwajima, *J. Am. Chem. Soc.*, **99**, 961 (1977); R. E. Donaldson and P. L. Fuchs, *J. Org. Chem.*, **42**, 2032 (1977)). (c) Although another type of cyclopropane ring cleavage to form allylic cation is possible (initiated by coordination of $TiCl_4$ with the acetal moiety of **5**), we have not detected any products of such an origin.

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(15) Attempts to detect a species like **13** on low temperature ^1H NMR have thus far been unsuccessful. We thank Professor T. Nakai and Mr. K. Tanaka for helping us to carry out the measurement.

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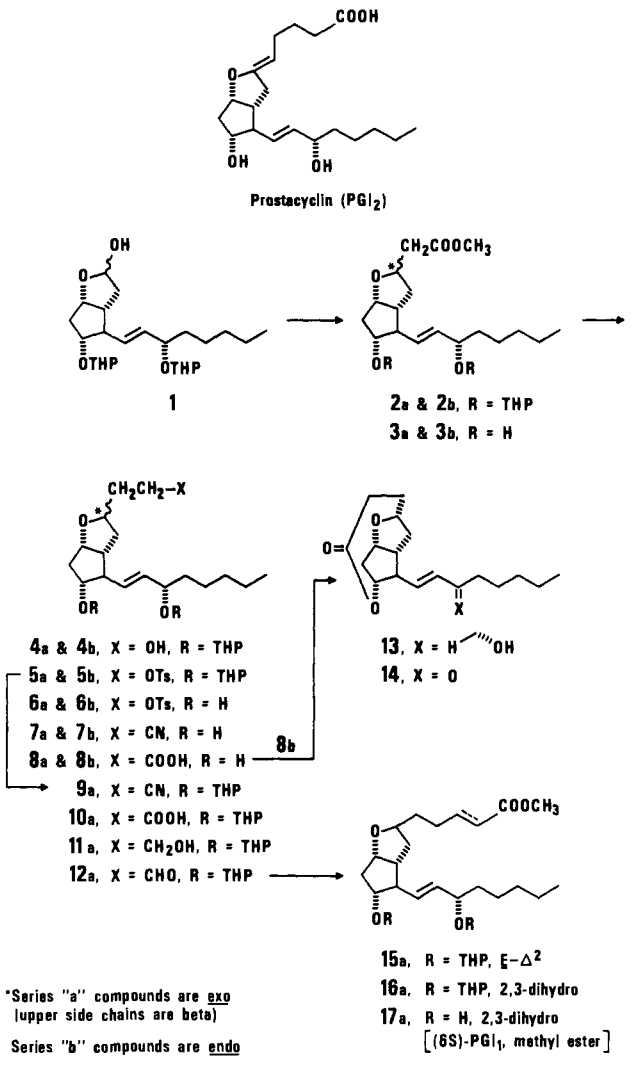
Received July 5, 1977



Stereoconfiguration of 5,6-Dihydroprostacyclins

Sir:

Recent communications have described the isolation,[1] biology,[1] synthesis, and stereochemistry[2-4] of prostacyclin (PGI_2),[5] a remarkable new prostaglandin which appears to have an important role in preventing thrombosis.[1] From a pharmaceutical standpoint, prostacyclin suffers a serious disadvantage in that it is rapidly hydrolyzed to the less active 6-oxo-$PGF_{1\alpha}$ even at pHs as high as 7.6.[2] Reduction of the acid-labile enol ether double bond should lead to chemically stable analogues (PGI_1s) which hopefully will retain the desirable characteristics of PGI_2. Past developments indicate that much effort will occur on the synthesis of PGI_1 analogues and it becomes desirable, therefore, to have a way of determining the configuration of isomers at C-6 by some simple procedure.[6] This communication describes an unambiguous assignment of configuration for PGI_1 isomers at C-6 and, in concert with Johnson's[4,6] NMR observations of PGI_1 isomers, a method of distinguishing such isomers in future analogues of PGI_1.

Reaction of lactol **1**[7] with trimethylphosphonoacetate and potassium *tert*-butoxide (tetrahydrofuran, 20 °C, 2 h) afforded 82% of a mixture of **2a** and **2b**, which was not readily separated by chromatography. Depyranylation (20:10:1 acetic acid–water–tetrahydrofuran at 40 °C for 4 h) of the mixture and repeated chromatographic purification (on E. Merck silica gel 60, 40–63 μ, 40–60% acetone in methylene chloride) gave 16% *endo*-carboxy side-chain isomer **3b** (mp 47–48 °C, R_f 0.41 on silica gel TLC plate with 4:6 acetone–methylene chloride) and 68% *exo*-carboxy side-chain isomer **3a** (R_f 0.35).[8]

To generate a definitive assignment of configuration at C-6 (prostaglandin numbering)[9] in these PGI_1 analogues, we set out to construct a short bridge between C-6 and C-11, a feat possible only with the isomer having the upper side chain in the endo configuration. Thus, **3a** and **3b** were repyranylated (dihydropyran, pyridine hydrochloride, 25 °C, 16 h) to give **2a** (R_f 0.59, silica gel plate, 1:1 ethyl acetate–hexane) and **2b** (R_f 0.67), respectively. Reduction of each isomer with lithium aluminum hydride gave **4a** and **4b**, respectively, each of which was treated with *p*-toluenesulfonyl chloride and pyridine (25 °C, 5 h) to give **5a** and **5b**. Depyranylation (as above) gave **6a** (84% from **3a**, R_f 0.33, silica gel plate, ethyl acetate) and **6b** (62% from **3b**, R_f 0.37), respectively. Each isomer (**6a** and **6b**) was treated with methanolic sodium methoxide and with potassium *tert*-butoxide in tetrahydrofuran in an effort to demonstrate formation of a cyclic ether[10] with one of them via an

intramolecular alkylation; however, neither isomer afforded such an ether.[11]

Treatment of **6a** and **6b** with sodium cyanide (hexamethylphosphoramide, 25 °C, 20 h) yielded **7a** (100%, R_f 0.50, silica gel plate, 1:1 acetone–methylene chloride) and **7b** (100%, R_f 0.51) which were saponified (potassium hydroxide, aqueous methanol) to give the 2,3-dinor-PGI_1 isomers **8a** (81%, R_f 0.32, silica gel plate, 1:1 acetone–methylene chloride containing 1% acetic acid) and **8b** (75%, R_f 0.39), respectively. Each acid was subjected to lactone formation using dipyridyl disulfide and triphenylphosphine.[12] Only one acid (**8b**, endo) afforded a lactone **13** (24%, R_f 0.41, silica gel plate, 6:4 ethyl acetate–hexane). To demonstrate lack of any unexpected rearrangements, the lactone was saponified back to its starting acid **8b**. Oxidation of **13** with manganese dioxide (ethyl acetate, 7 h) gave the expected unsaturated ketone **14** (69%, R_f 0.58, silica gel plate, 1:1 ethyl acetate–hexane) demonstrating conclusively the point of lactone formation.

We next turned our attention to relating our di- and trinor-PGI_1 analogues to the previously reported C-6 isomers of PGI_1.[2-4] The more plentiful isomer **5a** (exo upper side chain) was converted to **10a** (73%) via the nitrile **9a**[13] using methods described above. Reduction of **10a** with lithium aluminum hydride and Pfitzner–Moffatt oxidation[14] of the intermediate alcohol **11a** afforded the aldehyde **12a** (73% from **10a**, R_f 0.62, silica gel plate, 1:1 ethyl acetate–hexane). Reaction of **12a** with methyl (triphenylphosphoranylidine)acetate (tetrahydrofuran, 25 °C, 20 h) yielded **15a** (78%) which was hydrogenated with 5% palladium/carbon (ethyl acetate, atmospheric pressure, 0 °C) to yield **16a**.[15] Depyranylation of **16a** afforded (6*S*)-PGI_1 methyl ester (**17a**) (33% from **15a**, mp 42–43 °C, R_f 0.25 compared to 0.30 for the 6*R* isomer, silica gel plate, ethyl acetate). Compound **17a** was shown to be identical with one of the previously described C-6 isomers of PGI_1 methyl ester by melting point, mixture melting point, comparisons of TLC mobilities, and NMR and mass spectra. The other previously described isomer must then be the 6*R* or endo isomer.[16]

As first noted by Johnson and verified in our own work, PGI_1 and its analogues having the upper side chain in the exo configuration (series "a" compounds) exhibit an ill-defined quartet centered at δ 4.4–4.5 ($J \simeq 6$ Hz) in their NMR spectra ($CDCl_3$). The corresponding endo isomers have not shown this absorption and presumably incorporate this H signal further upfield as part of other multiplets. We have also noted that the endo isomer (6β H) of an isomer pair usually has a higher R_f on silica gel plates than the exo isomer (6α H). While these generalities have been derived (with no exceptions) from inspection of 18 pairs of PGI_1 analogues isomeric at C-6, caution should be used in new situations, particularly if there are overlapping NMR absorptions or drastic changes in molecular configuration.

Acknowledgment. We are indebted to Dr. John C. Sih for supplying samples of (6*R*)- and (6*S*)-PGI_1 methyl ester for comparison purposes.

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(5) Formerly called PGX and now, by agreement, PGI_2; see *Prostaglandins*, **13**, 375 (1977).
(6) The assignment of stereochemistry at C-6 of PGI_1 and derivatives has been based on stereochemical and mechanistic considerations and different conclusions have been arrived at by different authors; see ref 3, footnote 12 of ref 4, and the following footnote. Two recent references on conflicting assignments of C-6 configuration of dihydroprostacyclins were drawn to the attention of the author by referee (see ref 6a and 6b). Our work is in agreement with that of Fried and Barton who deduced stereochemical assignments on the basis of elegant mechanistic considerations, but appears to differ from Kovács' group who utilized ^{13}C NMR spectra for structural assignments. (a) J. Fried and J. Barton, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2199 (1977). (b) I. Tömösközi, G. Galambos, V. Simonidesz, and G. Kovács, *Tetrahedron Lett.*, 2627 (1977).
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(11) It is possible to construct a 6,9-cyclic ether emanating from **6b** (endo upper side chain) using molecular models; however, in actual practice it may not be possible to achieve the required transition state for cyclic ether formation.
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(14) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).
(15) Considerable overreduction occurred leading to 46% of the corresponding 2,3,13,14-tetrahydro compound.
(16) Our structural assignments for the C-6 isomers of PGI_1 methyl ester are in agreement with those of Johnson and colleagues[4] but appear to differ from those of Corey's group.[3]

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Received July 11, 1977

A New Amino Protecting Group Removable by Reduction. Chemistry of the Dithiasuccinoyl (Dts) Function[1]

Sir:

We wish to propose the 1,2,4-dithiazolidine-3,5-dione[2] heterocyclic system **1** as the basis of a new protecting group for peptide synthesis. These disulfide-containing amine derivatives are termed dithiasuccinoyl (Dts) amines by analogy with their carbocyclic analogues. Cleavage of the disulfide bond with thiols (or other reducing agents) generates the free amine (Scheme I). The reaction is driven to completion by loss of 2 equiv of gaseous carbonyl sulfide. The fact that both hydrogens of a primary amino function are replaced[3] is expected to be of particular advantage. Since the Dts-protecting group can be removed by mild reductive procedures, but is stable to acids and to photolysis above 330 nm, it is expected to lend itself to *orthogonal* systems[4] of peptide synthesis.

Some potential synthetic routes to Dts-amines are summarized in Scheme II. Chlorocarbonylsulfenyl chloride (**2**)[5] reacts[2a,d] in anhydrous solutions (optionally in the presence of tertiary amines) with ethyloxythiocarbonyl derivatives of primary amines **3**[6] to form an initial adduct **4**.[9] Ring closure to **5** followed by loss of ethyl chloride gives the Dts derivative **1**. The reactions proceed exceedingly rapidly at 0 to 45 °C, and in good yields.[10] Isocyanates **6** are the principal by-products. A new reagent, bis(chlorocarbonyl)disulfane (**7**)[11] was expected from a literature mechanism[2a] to react directly with primary amines to give the Dts derivative via the chlorocarbonyl carbamoyl disulfide intermediate **8**. However, the ring closure did not occur and isocyanates **6** were produced instead.

Scheme I