(14) D. Bethell, D. Whittaker, and J. D. Callister, *J. Chem. Soc.*, 2466 (1965).
(15) See, for example, M. T. H. Liu, O. Banjoko, Y. Yamamoto, and I. Moritani, *Tetrahedron*, 1645 (1975), and references therein.

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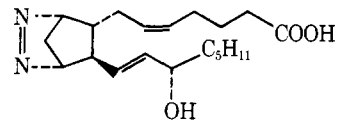
Received June 8, 1976

A Direct, Stereocontrolled Total Synthesis of the 9,11-Azo Analogue of the Prostaglandin Endoperoxide, PGH_2

Sir:

The 9,11-azo prostanoid **1** has recently been synthesized[1] and found to exhibit biological activity comparable to the naturally occurring prostaglandin (PG) endoperoxides PGH_2 (**2**) and PGG_2 (**3**)[2] in known test systems (e.g., with respect to human platelet aggregation and release reactions).[3] Interest in the synthetic azo analogue **1** has developed rapidly since its use provides a number of important advantages in the investigation of the biological effects of PG endoperoxides, and a wide variety of biological studies involving **1** are currently underway.[4] In contrast to the highly labile (and not easily available) PGG_2 and PGH_2 which rapidly decompose at 25 °C in neutral aqueous solution, **1** is very stable and convenient to use. Further, **1** is not subject to the rapid enzymic conversion to the highly active substance thromboxane A_2,[5] which is characteristic of PGG_2 and PGH_2 and which markedly complicates their study.



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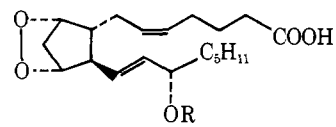
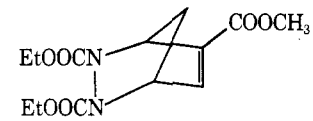


2, R = H
3, R = OH

The azo analogue **1** was originally synthesized[1] by a six-step sequence (overall yield ca. 11%) starting with PGA_2 methyl ester acetate.[6] Since it became clear that there would be a widespread and continuing demand for **1**, we have sought a more direct route, not dependent on the availability of PGA_2. An effective total synthesis by a novel route is reported here.[7] This process has obvious utility also for the synthesis of a large number of analogues of **1**.

The synthesis of the first key intermediate (**4**) for the construction of the desired azo analogue is not possible by the obvious route, a direct Diels–Alder reaction, since the required diene component is unavailable by direct preparation and in any event would be subject to rapid isomerization and dimerization. Nonetheless **4** could be prepared in good yield from the known mixture of dimers of methyl cyclopentadienecarboxylate[8] under carefully chosen conditions which allow both retro-Diels–Alder reaction to a mixture of monomers and formation of cross adducts with diethyl azodicarboxylate reversibly and under thermodynamic control. Specifically, upon heating 1 equiv of diethyl azodicarboxylate with 2.2 equiv of methyl cyclopentadienecarboxylate dimers in chlorobenzene (7 ml/g of azo ester) for 50 h at 125 °C under argon, **4** was formed without significant accompaniment by position isomers,[9] and could be isolated in 65% yield after column chromatography on silica gel using petroleum ether–ether (2:3) as eluent.[10] Reaction of **4** with various Gilman (cuprate) reagents derived from 3-[dimethyl-*tert*-butylsilyloxy]-*trans*-1-octenyllithium[11] at low temperatures (mildest possible conditions) produced only the product of conjugate addition plus subsequent elimination (**5**) and none of the desired bridged adduct (silyl ether corresponding to **9**). Conjugate addition of nitro-



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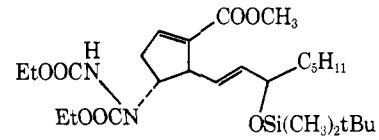

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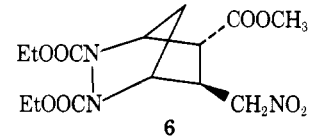
methane to **4** was successful under closely defined conditions, nitromethane–water–methanol (1:1. 8:1 by volume; total 6.3 ml/mmol of **4**), 4.25 h at 23 °C in the presence of a catalytic amount (0.1 equiv based on **4**) of 1,1,3,3-tetramethylguanidine,[12] to form **6** as a crystalline solid, mp 119–121 °C, in 71% yield.[13] Treatment of the nitro compound **6** in THF (10 ml/g) with 1.01 equiv of 0.1 N aqueous potassium hydroxide for 5 min at 0 to 5 °C, subsequent removal of THF under reduced pressure, and addition of 2 M aqueous magnesium sulfate (excess) followed by 0.05 M aqueous potassium permanganate (dropwise, 0.67 mol equiv based on **6**, reaction temperature 0–5 °C, vigorous stirring)[14] afforded after workup the aldehyde **7** in high yield. The stereochemistry of **7**, a crucial element in the synthesis and expected from previous experience,[15] was confirmed by proton magnetic double resonance spectra with spin decoupling ($J_{AB} \cong J_{BC} \cong 3.5$ Hz; $J_{CD} \cong 0$ Hz).



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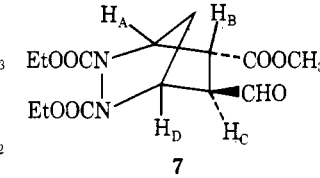

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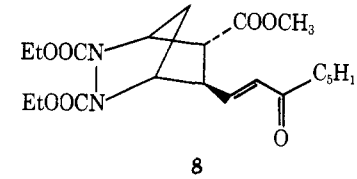

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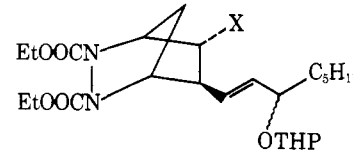
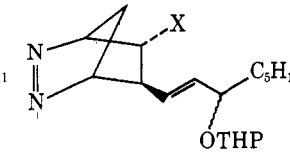
The aldehyde **7** was converted by the Emmons–Horner method[16] to the enone **8** (68% overall from **6**), and thence to a diastereomeric mixture of allylic alcohols (1.1 equiv of lithium selectride in THF at −78 °C for 30 min) and the corresponding tetrahydropyranyl ethers **9**[16] (95% from **8**). At this point in the synthesis, the successful accomplishment of the remaining structural modifications, generation of the azo

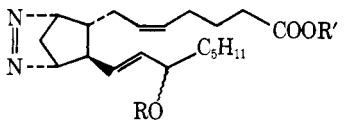


9, X = $COOCH_3$
10, X = COOH
11, X = CH_2OH



12, X = CH_2OH
13, X = CHO
14, X = CH=$CHOCH_3$
15, X = CH_2CHO

function and the PGH_2 carboxylic appendage, depended upon a crucial ordering of individual steps and careful selection of reagents and reaction conditions. Among the constraints which had to be reckoned with were (1) interference of N—COOEt groups with reagents such as R_2AlH, $LiBH_4$, and the ylide $Ph_3P{=}CHCH_2CH_2CH_2COO^-$ (under the usual conditions[16]), (2) acid sensitivity of azo-bridged intermediates, and (3) lability of **9** and **13** to base-catalyzed β-elimination of the nitrogen bridge. Under carefully selected conditions, the ester **9** was converted to the corresponding acid **10** (10 equiv of potassium hydroxide in H_2O-CH_3OH(1:2) at 0 °C for 18 h) and thence to the alcohol **11** by sequential treatment with ethyl chloroformate–triethylamine (1 equiv each, in THF at 0 °C for 30 min) and sodium borohydride (6 molar equiv in 6:1 THF-H_2O at 10–15 °C for 2 h). More vigorous base treatment of **11** (6.75 equiv of KOH in ethylene glycol at 115 °C for 4.5 h) removed both ethoxycarbonyl groups to form the corresponding free hydrazine which after extraction but without purification was directly oxidized by air in the presence of cupric acetate catalyst to the azo-bridged alcohol **12** (70% yield). oxidation of **12** by chromium trioxide–pyridine (1:2) reagent (8.5 equiv) in CH_2Cl_2 at 0 °C for 1.5 h yielded the corresponding (azo-bridged) aldehyde (**13**), which was directly converted to the enol ether **14** (70% from **12**) using 3 equiv of methoxymethylenetriphenylphosphorane (generated using lithium diisopropylamide in THF) in 3.4:1 toluene–THF at 0 °C for 0.5 h. The aldehyde **15** could only be obtained in poor yield from enol ether **14** by mild acid-catalyzed hydrolysis in water at 0 to 25 °C (even aqueous acetic acid) because of an extraordinary sensitivity to acid. However, the aldehyde was generated cleanly from **14** under *neutral* conditions (10:1 THF-H_2O, 3 equiv of mercuric acetate as catalyst at 23 °C for 10 min followed by addition of excess aqueous potassium iodide and extraction). Reaction of **14** with the Wittig reagent from (4-carboxybutyl)triphenylphosphonium bromide in Me_2SO[16] at 25 °C afforded the desired acid **16** (66% from **14**). Treatment of **16** with ethereal diazomethane followed by THP cleavage using 3:1:1 HOAc-THF-H_2O at 45 °C for 3 h gave a mixture of 15-epimeric (PG numbering) hydroxy esters **17** (99% yield) which were readily separable by chromatography



16, R′ = H; R = THP
17, R′ = CH_3; R = H

on silica gel into 15α- (natural configuration) and 15β-alcohols (R_f values 0.33 and 0.42, respectively, on silica gel plates with ether for development). Hydrolysis of the methyl ester of the 15α-alcohol (0.15 N lithium hydroxide in 2.5:1 THF-H_2O at 0 °C for 2.5 h) afforded upon isolation the (±)-azo analogue (**1**) of PGH_2 (99% yield), spectroscopically and chromatographically identical with an authentic sample synthesized from PGA_2.[1] The same product was obtained from the 15β-epimer of the ester **17** by mesylation (1.2 equiv of methanesulfonyl chloride and 1.2 equiv of triethylamine in CH_2Cl_2 at −25 °C for 1 h) followed by reaction with potassium superoxide[15,17] (6 equiv in 1:1:1 Me_2SO-DME-DMF containing 18-crown-6 for 20 min at 0 °C) (72% overall yield).[18,19]

References and Notes

(1) E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malmsten, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 3355 (1975).
(2) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 899 (1973).
(3) (a) M. Hamberg, J. Svensson, T. Wakabayashi, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 345 (1974); (b) M. Hamberg and B. Samuelsson, *ibid.*, **71**, 3400 (1974).
(4) These include investigations concerned with blood platelets, cardiovascular tissue, renin release from kidney, thyroid hormone release, and various forms of inflammation.
(5) M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 2994 (1975). See also, G. B. Kolata, *Science*, **190**, 770 (1975).
(6) For multistep syntheses of this substance see (a) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.*, **92**, 397 (1970); E. J. Corey and G. Moinet, *ibid.*, **95**, 6831 (1973); (c) E. J. Corey and J. Mann, *ibid.*, **95**, 6832 (1973).
(7) The azo analogue **1** and intermediates **4** through **17** were obtained by the route described herein in racemic form.
(8) Prepared by addition of cyclopentadienyl sodium (Arapahoe Chemical Co.) in THF to a mixture of excess dry ice (small pieces) and THF to form a dimeric mixture of cyclopentadiene carboxylic acids (see, J. Thiele, *Chem. Ber.*, **34**, 68 (1901)) and subsequent esterification using 4% sulfuric acid–methanol (4% by vol) at reflux for 4.5 h. See also, W. E. Franklin, C. H. Mack, and S. P. Rowland, *J. Org. Chem.*, **33**, 626 (1968).
(9) At shorter reaction times **4** was accompanied by substantial amounts of the isomeric adduct having the methoxycarbonyl group at the bridgehead carbon. At higher reaction temperatures yields of **4** were considerably lower, and appreciable contamination by the isomeric adduct was observed.
(10) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained using chromatographically homogeneous samples for all synthetic intermediates described herein. All reactions except those involving acidic reagents were conducted under an atmosphere of argon.
(11) See E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **94**, 7210 (1972).
(12) See G. P. Pollini, A. Barco, and G. De Guili, *Synthesis*, 44 (1972).
(13) Crude **4** taken directly from the Diels–Alder process can be used for the reaction with nitromethane, in which case pure **6** can be isolated after chromatography in 42% yield (overall for both steps).
(14) See H. Shechter and F. T. Williams, *J. Org. Chem.*, **27**, 3699 (1962).
(15) E. J. Corey, M. Shibasaki, K. C. Nicolaou, C. L. Malmsten, and B. Samuelsson, *Tetrahedron Lett.*, 737 (1976).
(16) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).
(17) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975); E. J. Corey, K. C. Nicolaou, and M. Shibasaki, *J. Chem. Soc., Chem. Commun.*, 658 (1975).
(18) The biological activity of racemic azo analogue **1** was one-half that of the optically active material synthesized as described in ref 1 from PGA_2 with regard to human platelet aggregation and release reactions. The racemic 15β-epimer of **1** showed essentially no biological activity in these tests. We are indebted to Drs. Bengt Samuelsson and Curt Malmsten of the Karolinska Institutet, Stockholm, for the biological data.

(19) This research was assisted financially by a Grant from the National Science Foundation.

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Received June 15, 1976

Optical to Electrical Energy Conversion: Cadmium Telluride-Based Photoelectrochemical Cells Employing Telluride/Ditelluride Electrolytes

Sir:

We wish to report a new result concerning the stabilization of n-type semiconductor photoelectrodes used in electrochemical cells for the conversion of optical energy to electricity.[1] In recent reports[2,3] we outlined in detail the stabilization of CdS- and CdSe-based photoelectrochemical cells by use of a sulfide or polysulfide containing electrolyte. The key result is that oxidation of the *added* sulfide or polysulfide occurs at the photoelectrode at the expense of photoanodic dissolution of the electrode which normally occurs as in reaction 1.

$$_{(\text{photoanode})}CdX_{(s)} \xrightarrow{2h\nu} Cd^{2+}{}_{(aq)} + X_{(s)} + 2e^- \qquad (1)$$

$$X = S, Se$$

Thinking that CdTe would be derivative, we attempted to use n-type CdTe as a photoelectrode and found it to be *unstable* even in a polysulfide electrolyte capable of stabilizing CdSe. The decomposition of a CdTe photoanode occurs according to reaction 1 for X = Te.[4] We now report that CdTe can be stabilized by an electrolyte additive. Importantly, we show that a stable CdTe-based cell is superior to CdS or CdSe in terms of wavelength response (onset at 865 nm vs. 520 and 750 nm