isocyanate (1.15 equiv) and triethylamine (1.12 equiv) in tetrahydrofuran (THF) at 25° for 4 hr to give, after filtration and washing with dilute aqueous acid and then brine, the racemic carbamate carboxylic acid **3a**,[5] mp 80–82°, in 94% yield. The acid **3a** upon treatment with (+)-amphetamine yielded a crystalline salt which could be fully resolved by one or two recrystallizations from isoamyl acetate–ethyl acetate (2:1); the fully resolved salt, mp 149–150°, had $[\alpha]^{20}D$ −58° (*c* 1.16 in CH_3OH). The resolved form of **3a**, mp 129–130°, $[\alpha]^{20}D$ −55.5° (*c* 1.02 in $CHCl_3$), obtained from the salt by treatment with aqueous acid and extraction, was converted quantitatively to the methyl ester **3b**, mp 100°, $[\alpha]^{20}D$ −54° (*c* 1.0 in $CHCl_3$), using diazomethane. Removal of the trichloroethyl group in **3b** was accomplished using powdered zinc–copper couple in methanol containing a little zinc chloride at 30–40° for 18 hr to give 92% of the hydroxy urethane **3c**, mp 138–139°, $[\alpha]^{20}D$ −23° (*c* 0.98 in $CHCl_3$). Collins oxidation of alcohol **3c** at −20° produced the corresponding aldehyde which was condensed with the sodium salt of dimethyl 2-oxoheptylphosphonate[1a] to form the enone **4**, mp 124–125°, $[\alpha]^{20}D$ −85.5° (*c* 1.0 in $CHCl_3$) (65% yield overall), reduction of which with the cyclic trialkylborohydride derived from thexylborane and limonene[1c,1g] gave a predominance[1g] (91%) of the 15.*S* alcohol **5a**, mp 144–145°, $[\alpha]^{20}D$ −43.5° (*c* 1.0 in $CHCl_3$) together with a small amount (9%) of the 15-*R* isomer, mp 117–118°, $[\alpha]^{20}D$ −57.5° (*c* 0.96 in $CHCl_3$); the diastereomers were readily separated by chromatography on silica gel with the 15-*S* isomer **5a** having the higher R_f. The methyl ester **5a** was saponified in 93% yield to the corresponding acid **5b**, mp 150–151°, $[\alpha]^{20}D$ −41.5° (*c* 1.13 in CH_3OH), by exposure to 0.1 *N* sodium hydroxide in THF–water (5:1) at 25° for 8 hr.

The role of the *p*-arylurethano unit in the synthesis was now completed in a key step in which the heterolysis of that group provided the driving force for lactonization of the acid **5b**. This reaction was effected simply by heating a solution of **5b** in water–dimethoxyethane (4:1) buffered to pH 7 at reflux for 18 hr to produce the hydroxy lactone **6a** as a colorless oil, $[\alpha]^{20}D$ +275° (*c* 1.36 in $CHCl_3$), ν_{CO} 1770 cm^{-1} (84% yield). The tetrahydropyranyl derivative[1a] **6b** (found in 99% yield), $[\alpha]^{20}D$ +191.2° (*c* 1.1 in $CHCl_3$), was reduced[1a] with diisobutylaluminum hydride in toluene at −78° to form the oily lactol **7**, $[\alpha]^{20}D$ +140.5° (*c* 1.1 in $CHCl_3$) which upon treatment with the Wittig reagent derived from 5-triphenylphosphoniovalerate ion in dimethyl sulfoxide[1a] yielded the oily hydroxy acid **8**, $[\alpha]^{20}D$ +123° (*c* 1.25 in $CHCl_3$). Collins oxidation of **8** at −23° (with work-up by stirring with $NaHSO_4$ at −23° for 30 min, filtering, and evaporation) followed by cleavage of the tetrahydropyranyl group using acetic acid–water (3:1) at 40° for 4 hr afforded prostaglandin A_2 (**9**), $[\alpha]^{20}D$ +140° (*c* 1.15 in $CHCl_3$), as a colorless oil indistinguishable from natural material (isolated from *Plexaura homomalla*), $[\alpha]^{20}D$ + 131° (*c* 1.26 in $CHCl_3$), in nmr, infrared and ultraviolet absorption, and in thin-layer chromatographic behavior with several solvent systems.

The synthetic route to A prostaglandins described herein possesses several attractive features. The resolution step is unusually facile and is accomplished early in the sequence. Most of the intermediates are easily purified, crystalline solids and the yields are uniformly good. From the resolved intermediate **3c** there is ready access to PGA analogs in which one or both side chains are varied.[6]

(5) Satisfactory spectroscopic and analytical data were obtained on each of the intermediates reported herein.

(6) This work was assisted financially by the U. S. National Institutes of Health and the CNRS of France. The receipt of a NATO travel grant by G. M. is also gratefully acknowledged.

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A New Stereocontrolled Synthesis of Prostaglandins *via* Prostaglandin A_2

Sir:

We report herein a new synthetic approach to prostaglandins which depends in the key step on the attachment of the C-13 to C-20 chain (prostanoic acid numbering) by cross coupling of a vinylic copper reagent with an allylic electrophile.[1] In this step the site of attack on the allylic substrate is enforced with remarkable effectiveness by the presence of a dimethyl-*tert*-butylsilyl (DMBS) screening group. Further, the stereochemical outcome is determined by the presence of an anionic leaving group, introduced with rigid stereochemical control, which is prone to attack by an organometallic nucleophile at carbon (inversion) rather than at the group itself.[2] The new synthesis is designed to lead directly to A type prostaglandins (PGA's) in contrast to most of the recently developed approaches which afford E or F prostaglandins directly and PGA's by further transformation.[3]

The (±)-lactone **1**[4] is readily available in three steps from cyclopentadiene.[5] Hydrolysis of **1** with 1 equiv of aqueous base, acidification to pH 3.5–4 at 0° in the presence of ethyl acetate, extraction with cold ethyl acetate, and drying at 0° afforded solutions of the corresponding hydroxy acid. Addition of (+)-α-methylbenzylamine (*ca.* 5% excess) at 0° led to rapid formation of the crystalline salt **2** which could be easily purified to constant rotation, $[\alpha]^{18}D$ −25.4° (*c* 0.7 in CH_3OH) and mp 133–134°, by one or two recrystallizations from ethyl acetate containing a few per cent methanol (chloroform or ethyl acetate alone may also be used for recrystallization).[6] Extraction of a solution of

(1) For cross coupling of organocopper reagents with allylic electrophiles, see (a) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); **90**, 5615 (1968) (halides); (b) P. Rona, L. Tökes, J. Tremble, P. Crabbé, *Chem. Commun.*, 43 (1969) (acetates); (c) R. J. Anderson, *J. Amer. Chem. Soc.*, **92**, 4978 (1970); R. W. Herr and C. R. Johnson, *ibid.*, **92**, 4979 (1970) (epoxides).

(2) Attack on the leaving group could lead to substitution with retention of configuration by the type of process recently demonstrated for the reaction between certain organometallic nucleophiles and halides. See G. S. Kaermer, M. L. Hall, and T. G. Traylor, *ibid.*, **94**, 7205 (1972), and H. G. Kuivila, J. L. Considine, and J. D. Kennedy, *ibid.*, **94**, 7206 (1972).

(3) For other direct routes to PGA's, see (a) E. J. Corey and P. A. Grieco, *Tetrahedron Lett.*, 107 (1972); (b) J. Martel, E. Toromanoff, J. Mathieu, and G. Nomine, *ibid.*, 1491 (1972).

(4) E. J. Corey, Z. Arnold, and J. Hutton, *ibid.*, 307 (1970).

(5) We are indebted to Dr. A. Brossi and the Hoffman-La Roche Co. for providing a large quantity of 1.

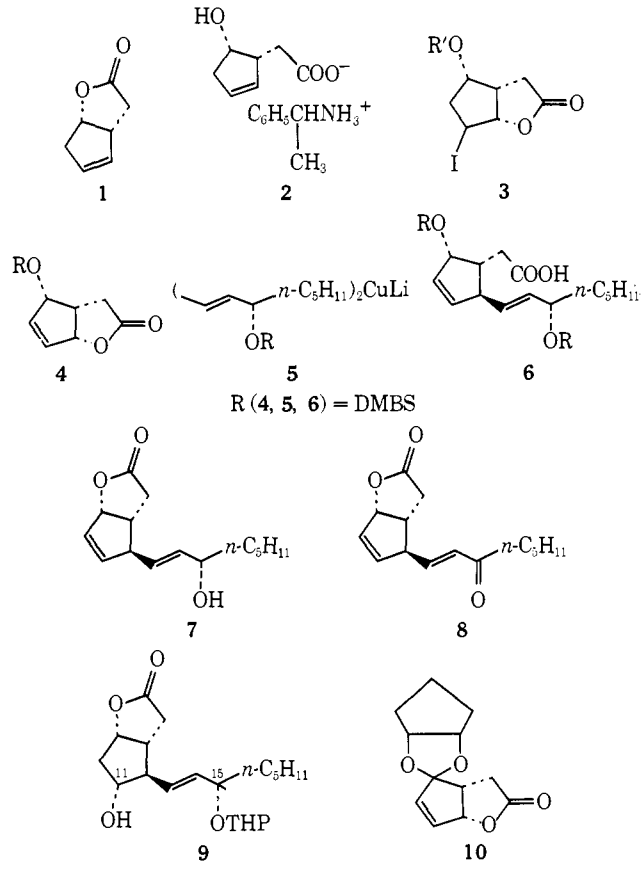
(6) The ease of resolution of the hydroxy acid corresponding to 1 adds further to its attractiveness as a starting material for the synthesis of prostanoids.

2 in aqueous base (1 equiv) with ether to remove α-methylbenzylamine followed by reaction of the aqueous phase at pH 5 and 20° with 2.5 equiv of iodine afforded the iodolactone **3** (R′ = H)[7a] (85%)[8] as an oil which was treated directly with dimethyl-*tert*-butylsilyl chloride (1.5 equiv) and imidazole (2 equiv) in dimethylformamide[9] at 35° for 22 hr to give the silyl ether **3** (R′ = DMBS),[7] as a colorless oil (85%), $[\alpha]^{18}D$ +28.5° (*c* 1.05 in $CHCl_3$). Exposure of this silyl ether to 1,5-diazabicyclo[4.3.0]non-5-ene[10] (1 equiv) in tetrahydrofuran at 70° for 2 hr under argon led to elimination of HI to form the unsaturated lactone **4**,[7] $[\alpha]^{14}D$ −25.5° (*c* 1.86 in $CHCl_3$), isolated in 94% yield as a colorless liquid.

The unsaturated lactone **4** was treated with an equimolar quantity of the organocopper reagent **5** (*S* configuration, *vide infra*) in ether–pentane (*ca.* 2:1, 7 ml/mmol of **4** total volume) under argon at −78 to −60° for 1 hr, −60 to −40° for 1 hr, and finally at −40 to −20° for 1 hr (reaction complete). The mixture was cooled to −50° and quenched with methanol. The coupling product **6**, obtained from this mixture by partitioning between saturated aqueous ammonium chloride–ether and concentration of the ether phase, was directly converted to the hydroxy lactone **7** by heating with 1:1 acetone–0.2 *M* aqueous hydrochloric acid at 55–60° for 2 hr. Purification was effected by saponification of **7** with 1.5 equiv of lithium hydroxide in 1:1 dimethoxyethane–water at 5°, extraction with ether to remove nonacidic material, acidification to pH 3, and extraction with ethyl acetate. The product contained in the extract underwent clean acid-catalyzed cyclization after several hours at 25° to afford the pure lactone **7**[7,8] (*ca.* 80% yield), $[\alpha]^{18}D$ +252° (*c* 0.2 in $CHCl_3$), as a colorless oil identical in all respects with a specimen of **7** produced by an independent and unambiguous synthetic route.[11] Further, oxidation of **7** using activated manganese dioxide produced the enone **8**[7] which was identical spectroscopically and chromatographically with a sample of **8** synthesized in these laboratories from the known substance **9** by the sequence: **9** → 11-tosylate (TsCl–pyridine) → $\Delta^{10,11}$ olefin (base) → 15-alcohol ($HOAc-H_2O$) → 15-ketone **8** (MnO_2).[12]

Careful chromatographic examination of the mixture produced by reaction of **4** and **5** did not reveal the presence of the coupling product corresponding to SN2′ mode of reaction. In contrast, however, we have observed that reaction of the cuprate **5** with the ketal **10** proceeds to give comparable amounts of SN2 and SN2′ products. The observed selectivity for SN2 product in the case of substrate **4** would appear to be a consequence of the bulk of the *tert*-butyldimethylsilyloxy group and a preference for cis stereochemistry in the SN2′ process.[13]

The vinylic copper reagent **5** required for the above described coupling was prepared from the corresponding vinylic lithium reagent along lines previously described,[14] starting from the corresponding vinylic iodide



1 2 3 4 5 6 7 8 9 10

(obtained essentially by the method of the Syntex group[15]).

The conversion of **7** to prostaglandins which is described elsewhere,[11] taken together with the work described herein, constitutes a synthesis of the major prostaglandins of the second series, PGA_2, PGE_2, and $PGF_{2\alpha}$. This route to prostaglandins is short and simple, completely stereocontrolled, and, as indicated earlier, affords the A prostaglandin directly rather than indirectly. It should be of value in the synthesis of PGA analogs having modified side chains, substances which are currently of great medical interest.[16]

(7) Satisfactory (a) infrared, proton magnetic resonance, and (b) mass spectral data were obtained for this intermediate.
(8) Yield not optimized.
(9) E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972).
(10) H. Oediger, F. Möller, and K. Eiter, *Synthesis*, 591 (1972).
(11) E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, **95**, 6831 (1973).
(12) The first two steps of this sequence were performed by Dr. Shiro Terashima.
(13) See G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).
(14) E. J. Corey and D. J. Beames, *ibid.*, **94**, 7210 1972).
(15) A. F. Kluge, K. G. Untch, and J. H. Fried, *ibid.*, **94**, 7827 (1972). In our work (*S*)-(−)-oct-1-yn-3-ol [J. Fried, C. H. Lin, M. M. Mehra, and P. Dalven, *Ann. N. Y. Acad. Sci.*, **180**, 38 (1971)] was converted to the *tert*-butyldimethylsilyl ether,[9] hydroborated with 9-borabicyclo[3.3.1]-nonane to afford a vinylborane which yielded the vinylic iodide by successive treatment with trimethylamine oxide and iodine.
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Effects of Halogen Substituents on the Intrinsic Acidity of Acetic Acids Determined by Measurements of Gas-Phase Ion Equilibria

Sir:

Recently[1] we reported results for the gas-phase equilibria (1) measured with a pulsed electron beam high-

(1) R. Yamdagni and P. Kebarle, *J. Amer. Chem. Soc.*, **95**, 4050 (1973).