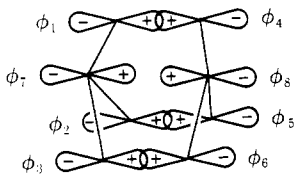
again entirely equivalent to that in cyclobutadiene. Thus, since **1** is isoconjugate with the cyclobutadiene, dication $(CH)_4^{2+}$ should be aromatic. Whereas the parent cyclobutadiene dication was not yet observed under stable ion conditions, the tetramethylcyclobutadiene dication **10**[12a] as well as the tetraphenyl dication **11**[12b] were reported as stable 2π-aromatic systems. The lesser stability of **8a** can then be attributed to the overlap of the "empty" 2p atomic orbitals being less efficient than that of ϕ_7 and ϕ_8 in **9** (in addition, of course, to the adverse steric effect in **8a**) and the lesser stability of **3** to the absence of aromaticity. In order to relieve the unfavorable electrostatic repulsion be-



9

tween positive charges in **1**, MINDO/3 indicates that more than half of the charge is delocalized to the 12 hydrogen atoms with the charge at the cation centers, comparable to that found for the monocation **6**. Calculations seem to indicate that dication **1** thus approximates a doubly charged sphere with the positive charge distributed over its surface.[13]

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(12) (a) G. A. Olah, J. M. Bollinger, and A. M. White, *J. Amer. Chem. Soc.*, **91**, 3667 (1969); (b) G. A. Olah and Gh. D. Mateescu, *ibid.*, **92**, 1430 (1970).

(13) An interesting report on bridgehead halide exchange appeared in which the dichloride **5** had been converted at room temperature to the corresponding diiodide. The mechanism, however, of this halogen exchange is still unclear. See, J. W. McKinley, R. E. Pincock, and W. B. Scott, *J. Amer. Chem. Soc.*, **95**, 2030 (1973).

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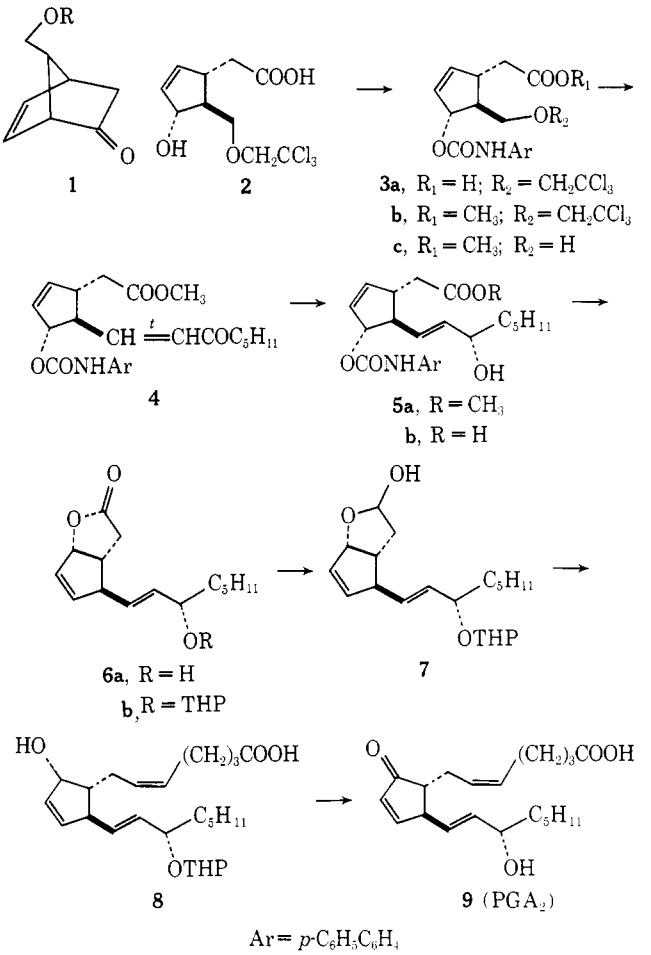
Direct, Stereocontrolled Synthesis of A Prostaglandins Using the Bicyclo[2.2.1]heptene Approach

Sir:

Earlier papers from this laboratory have described general and direct syntheses of all the primary (F_α and E) prostaglandins from a common intermediate.[1] We report here a novel modification of the general scheme which leads *directly* to A prostaglandins with stereochemical control. This route is of special practical value for the synthesis of analogs of A prostaglandins, currently of considerable interest in regard to medical treatment of hypertension. Further, since a stereocontrolled and efficient route from A prostaglandins to primary prostaglandins is now available,[2] this approach can even be applied to the generation of E and F type structures.[3]

The ketone **1** is available from thallous cyclopentadienide and bromomethyl 2,2,2-trichloroethyl ether without isolation of intermediates in 92% overall yield.[1c,e] Reaction of **1** either with peracid followed by aqueous base or with alkaline hydrogen peroxide[4] affords the hydroxy acid **2** in >95% yield (Scheme I). For storage,

Scheme I



the acid labile **2** was converted to the crystalline ammonium salt by reaction in ether with ammonia gas. This ammonium salt was converted quantitatively to the *tert*-butyldimethylsilyl ester by stirring for 5 hr at 25° with an equivalent of *tert*-butyldimethylsilyl chloride, and the resulting ester was treated with *p*-phenylphenyl

(1) See (a) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinschenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970); (b) E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, **92**, 2586 (1970); (c) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, **93**, 1491 (1971); (d) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971); (e) E. J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4326 (1971); (f) E. J. Corey and R. K. Varma, *ibid.*, **93**, 7319 (1971); (g) E. J. Corey, K. B. Becker, and R. K. Varma, *ibid.*, **94**, 8616 (1972); (h) E. J. Corey and T. K. Schaaf, *J. Org. Chem.*, **37**, 2921 (1972); (i) E. J. Corey, *Ann. N. Y. Acad. Sci.*, **180**, 24 (1971).

(2) E. J. Corey and H. E. Ensley, *J. Org. Chem.*, **38**, 3187 (1973).

(3) For a different and complimentary stereocontrolled synthesis of A prostaglandins see E. J. Corey and J. Mann, *J. Amer. Chem. Soc.*, **95**, 6832 (1973).

(4) N. M. Weinschenker and R. Stephenson, *J. Org. Chem.*, **37**, 3741 (1972).

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.