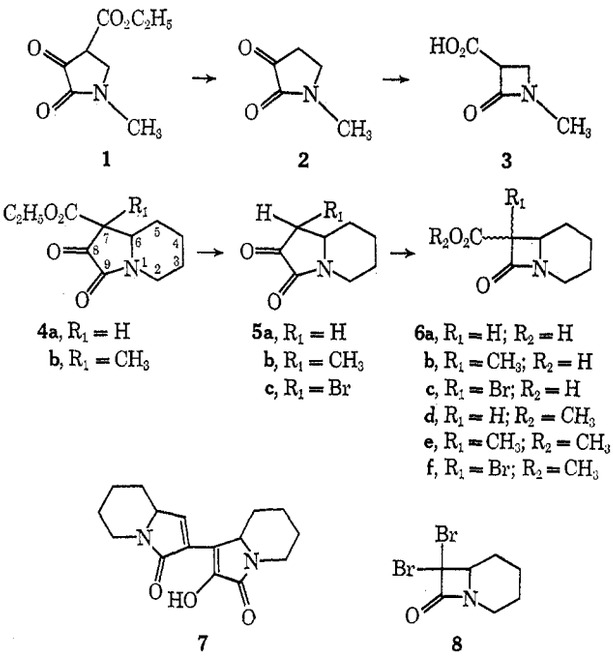
procedure (reflux time 2.5 hr). Chromatographing **5a** on silica with $CHCl_3$ resulted in self-condensation to **7** [mp 219–224° dec; nmr δ 0.8–2.5 (m, 12 H), 2.6–3.2 (m, 2 H), 3.7–4.5 (m, 4 H), 6.59 (d, J = 2.2 Hz, 1 H), 12.9 (s, 1 H); uv (C_2H_5OH) 249 nm (ε 12,300), 297 (14,200)], a facile self-condensation also observed with other α-keto-γ-lactams.[5] Reaction of **5a** with excess periodate in lithium phosphate buffer (pH 6.3) was complete in 20 min, determined by the decrease in absorbance at 223 nm, and crystallization (acetone–hexane) of the extracted product gave 7-carboxy-8-oxo-1-azabicyclo[4.2.0]octane (**6a**): 70%; mp 145–146°; nmr δ 1.1–2.3 (m, 6 H), 2.5–3.1 (m, 1 H), 3.5–4.1 (m, 2 H), 3.75 (d, J = 1.8 Hz, 1 H), 9.2 (s, 1 H); ir 1753, 1722 cm^{-1}.[8] The 1.8-Hz coupling constant establishes the C-6 and C-7 protons as trans;[9] no evidence for any cis isomer was found. Esterification of **6a** with diazomethane gave **6d** and gas chromatography[10] of this ester gave a single symmetrical peak.

7-Ethoxycarbonyl-7-methyl-1-azabicyclo[4.3.0]nonane-8,9-dione (**4b**, mp 92–93°), obtained[11] in 30% yield by refluxing for 18 hr a benzene solution of diethyl 3-methyl-2-oxosuccinate[12] with an ether–ethanol solution of 2 molar equiv of 1-piperidiene,[13] was hydrolyzed and decarboxylated as described for the synthesis of **2** (reflux time 1.5 hr), resulting in 7-methyl-1-azabicyclo[4.3.0]nonane-8,9-dione (**5b**, 74%, mp 191–193°). Reaction of **5b** with periodate gave 7-carboxyl-7-methyl-8-oxo-1-azabicyclo[4.2.0]octane (**6b**): 50%; mp 179–181°; ir 1743, 1713 cm^{-1}; nmr δ 1.2–2.1 (m, 6 H), 1.52 (s, 3 H), 2.5–3.0 (m, 1 H), 3.6–4.0 (m, 2 H), 10.6 (s, 1 H). Gas chromatography of **6e** methyl ester (ir 1756, 1725 cm^{-1}), obtained from **6b** with diazomethane, gave a singly symmetrical peak.[10]

The bromo analog, 7-bromo-1-azabicyclo[4.3.0]-nonane-8,9-dione (**5c**, mp 121–122° from chloroform–hexane), obtained in 80% yield from **5a** by reaction with cupric bromide in methylene chloride and treated with periodate as previously described, gave a 40% yield of 7-bromo-7-carboxy-8-oxo-1-azabicyclo[4.2.0]-octane (**6c**) as a mixture of stereoisomers. Gas chromatography[10] of **6f** methyl esters (obtained from **6c** with diazomethane) indicated the presence of two isomers in the ratio of 1:9. Also present were products subsequently shown to arise from decomposition of the minor isomer of **6f** during gas chromatography; no decomposition of the major isomer took place. Column chromatography on kieselgel with 3:1 ether–petroleum ether (bp 30–60°) permitted establishing the structures of the two major decomposition products as 7,7-dibromo-8-oxo-1-azabicyclo[4.2.0]octane (**8**) [mp 73–74°; nmr δ 1.2–2.3 (m, 6 H), 2.5–3.1 (m, 1 H), 3.5–4.0 (m, 2 H); ir 1782 cm^{-1}] and **6d**. The two isomers



of **6f**, separated by column chromatography on kieselgel with 3:1 ether–petroleum ether, were hydrolyzed to the respective acids **6c** with 1 equiv of potassium hydroxide in 50% aqueous dioxane (room temperature, overnight). The major isomer had double mp 97 and 119–120°; nmr δ 1.2–2.2 (m, 6 H), 2.6–3.1 (m, 1 H), 3.6–4.1 (m, 2 H); ir 1772, 1724 cm^{-1}. The minor isomer had mp 180–182°; nmr δ 1.1–2.3 (m, 6 H), 2.6–3.1 (m, 1 H), 3.6–4.1 (m, 2 H); ir 1777, 1719 cm^{-1}.

Formation of β-lactams by this oxidative ring contraction reaction thus proceeds under mild conditions and appears to be generally applicable. The method provides a route for introduction of difunctionality at the α position of the β-lactam and is compatible with the presence of a number of substituents. Its scope is being further investigated.

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RECEIVED JULY 2, 1973

(8) Both the cis and trans isomers of the ethyl and *tert*-butyl esters of **6a** have been synthesized by a different method: G. Lowe and J. Parker, *Chem. Commun.*, 577 (1971).

(9) H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Lett.*, 941 (1964); K. D. Barrow and T. M. Spotswood, *ibid.*, 3325 (1965).

(10) Chromatography was carried out on a 5 ft × 0.25 in. column of 5% QF-1 on Chromosorb W (80–100), AW-DMCS, at 175° and a He flow rate of 132 ml/min: T_R of **6e** = 3.9 min; T_R of **6d** = 4.3 min; T_R of **6f** (major) = 7.1 min; T_R of **6f** (minor) = 8.1 min.

(11) Based on the method used for the synthesis of 6-ethoxycarbonyl-1-azabicyclo[3.3.0]octane-7,8-dione: B. M. Goldschmidt, *J. Org. Chem.*, **27**, 4057 (1962).

(12) C. Clerc-Bory and C. Mentzer, *Bull. Soc. Chim. Fr.*, 436 (1958).

(13) Prepared by following the procedure used for the synthesis of 1-pyrroline: D. W. Fuhlhage and C. A. Van der Werf, *J. Amer. Chem. Soc.*, **80**, 6249 (1958).

A Versatile Prostaglandin Synthesis. Use of a Carboxy-Inversion Reaction

Summary: Ring contraction of the dione **5** gave the cyclopentenone **6** which was readily elaborated to the mixed peranhydride **17**; the latter then is transformed *via* a carboxy inversion reaction to **18**, a known precursor leading to the racemic prostaglandins E_2 and $F_{2\alpha}$.

Sir: By elimination of the hydroxyl group at the C-11 position in PGE_1 or PGE_2 to give either the PGA or 11-deoxy derivatives, the effects associated with the PGE compounds, *e.g.*, smooth muscle and antilipolytic properties, have been lost whereas the effect on blood

pressure has been retained or even intensified.[1] This observed separation of activities makes the C-11 position an interesting one for further modification.

Of the various total syntheses of the natural prostaglandins there are none which may be easily adapted to the preparation of ring analogs at the C-11 position while at the same time allowing for modifications of both side chains.[2] This communication describes such a scheme.

Treatment of 5-carboxy-1,3-cyclohexanedione (**1**)[3] with allyl alcohol and a catalytic amount of *p*-toluenesulfonic acid produced 3-allyloxy-5-(2-propenyloxycarbonyl)-2-cyclohexen-1-one (**2**). Refluxing crude **2** in acetic anhydride[4] for 8 hr afforded the rearranged enol acetate **3** which when treated with 1 equiv of lithium methoxide in methanol gave the dione **4**[5,6] (70% overall yield from **1**), mp 133–134°. Chlorination with 1 equiv of *tert*-butyl hypochlorite in methanol at 0° produced the chloro derivative **5**[5–7] (95%), bp 130° (0.01 mm), which was smoothly converted by treatment with 10 equiv of sodium carbonate in refluxing mesitylene for 1.5 hr to the ring-contracted[8] cyclopentenone **6**[5,6] (78% yield), uv max 226 nm (ϵ 7790), bp 84–86° (0.01 mm).

Reaction of the ketone **6** with excess nitromethane and a catalytic amount of "Triton B" for 3.5 hr at 65° yielded the 1,4 adduct **7**[5,6] (88% yield), purified on a 5:1 silica gel column using 5% ethyl acetate–benzene as eluent (homogeneous by tlc and gas chromatographic analysis). Oxidation of the allyl side chain with 1.1 equiv of sodium permanganate in a sulfuric acid–water–acetone solution gave the acid derivative **8**[5,6,9] (83% yield), mp 149–150°. Treatment of **8** with 1.1 equiv of lithium methoxide and 4 equiv of sodium borohydride in methanol afforded a mixture of alcohols which, after refluxing for 1 hr in THF followed by extraction of the residue with sodium bicarbonate, gave the lactone **10**[5,6] (carbonyl absorption ($CHCl_3$) at 5.6 and 5.72 μ, mp 102–103° (54% based on starting ketone **8**). Acidification of the bicarbonate solution afforded the alcohol **9**,[5,6] mp 98–100°. The alcohol **9** may be recycled by oxidation with 1.1 equiv of permanganate to give the starting ketone **8**. Alternatively the reduction of **8** with 2 equiv of lithium perhydro-9b-boraphenalylhydride[10] in THF at −78° showed a high degree of selectivity and produced a single alcohol (compound **9** was not detected by tlc) which was converted as previously described to the lactone **10** (88% yield). A confirmation of the stereochemical orientation shown for **10** was obtained from an X-ray analysis of a *p*-bromoanilide derivative, mp 189°, obtained from the acid **11**,[5,6] mp 125–126° (from hydrolysis of **10** in a dilute sulfuric acid–tetrahydrofuran solution at reflux for 24 hr).

We next turned our attention to the elaboration of the allylic alcohol side chain. Treatment of **10** with 1.1 equiv of lithium methoxide in methanol at 0° gave the lithium nitronate which after drying (high vacuum for several hours) was dissolved in a saturated aqueous solution of sodium tetraborate[11] and oxidized with 0.95 equiv of sodium permanganate[12,13] at 0° to give the aldehyde **12**[5,6] (70%), mp 93–94°. The aldehyde **12** was smoothly converted to the *trans*-enone lactone **13**[5,6] (70% yield), uv max 224 nm (ϵ 15,900), mp 48–49°, by treatment with the sodio derivative of dimethyl-2-oxoheptylphosphate in dimethoxyethane at 25° for 1.5 hr.[14] Reduction of the enone **13** with excess zinc borohydride in dimethoxyethane at 20° for 1 hr afforded a 95% yield of the 15α-hydroxy-11α-methoxycarbonyl lactone[15] (**14**) and the 15β isomer (ratio of ~1:1). The desired 15α isomer **14**,[5,6] mp 58–61°, was separated from the mixture by chromatography on silica gel using ether as the eluent. Saponification of **14** in a methanol–water (9:1) solution containing 2.2 equiv of sodium hydroxide at 50° for 1 hr gave after acidification and refluxing for 1 hr in THF the oily acid **15**[5,6] (92% yield). Acetylation of **15** with pyridine and acetic anhydride produced the 15α-acetoxy derivative **16**[5,6] (93% yield), mp 34–36°. Treatment of **16** with 1 equiv each of dicyclohexylcarbodiimide[16] and *m*-chloroperbenzoic acid (>98%) in ether–methylene chloride (1:1) at 0° for 15 hr produced the mixed peranhydride **17**[5,6] (61% yield), mp 79–80°, which, when refluxed in acetonitrile for 1.5 hr, undergoes a carboxy-inversion[17] reaction with *retention of configuration*[18] to give, after treatment with lithium methoxide (1 equiv) of the resultant mixed carbonate, the diol **18**[5,6] (35% yield). Compound **18** was identical in all respects with an authentic sample.[19] This intermediate has previously been converted to the racemic prostaglandins $F_{2\alpha}$ and E_2.

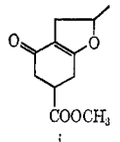
Compound **14** has been used to prepare 11-deoxy-11-carboxyprostaglandins as well as other 11-deoxy C-11 analogs[20] derived *via* modification of the carboxy group.

(1) J. E. Pike, F. P. Kupiecke, and J. R. Weeks in "Nobel Symposium 2 Prostaglandins," S. Bergstrom and B. Samuelson, Ed., Interscience, New York, N. Y., 1966.

(2) For leading references to active side chain analogs, see A. P. Labhsetwar, *Nature*, **238**, 400 (1972); E. W. Yankee and G. L. Bundy, *J. Amer. Chem. Soc.*, **94**, 3651 (1972); B. J. Magerlein, The 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, Topics in Medicinal Chemistry Symposium.

(3) E. E. van Tamelen, *J. Amer. Chem. Soc.*, **78**, 4405 (1956).

(4) When the rearrangement is carried out in solvents other than acetic anhydride, a substantial quantity of the dihydrofuran (i) is formed.



i

(5) Ir and nmr (at 60 MHz) spectra were in agreement with the assigned structure.

(6) Satisfactory elemental or mass spectral analytical data were obtained.

(7) The nmr spectra indicates the product to be a mixture of two isomers (ratio of 3:1).

(8) G. Büchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971). A similar ring contraction has recently been employed for the preparation of (±)-11-deoxyprostaglandin [J. Bagli and T. Bogri, *Tetrahedron Lett.*, 3817 (1972)].

(9) Preliminary experiments using (+) -and (−)-α-phenylethylamine afforded the (+) acid, mp 112–113°, $[\alpha]^{25}D$ +84.28° (*c* 1.01, CH_3OH), and the (−) acid, mp 111–112°, $[\alpha]^{25}D$ −79.9° (*c* 1.15, CH_3OH).

(10) H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, **92**, 709 (1970).

(11) If the sodium tetraborate was not employed (pH 9–10), the aldehyde **12** was always contaminated with nitro derivative **10**.

(12) H. Shechter and F. T. Williams, Jr., *J. Org. Chem.*, **27**, 3699 (1962).

(13) The lithium nitronate under various conditions of the Nef reaction always resulted in incomplete conversion and the contamination of the aldehyde **12** with substantial quantities of the starting nitro derivative **10**.

(14) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(15) Prostaglandin numbering.

(16) F. D. Greene and J. Kazan, *J. Org. Chem.*, **28**, 2168 (1963).

(17) D. B. Denney and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965).

(18) T. Kashiwagi, S. Kozuka, and S. Oae, *Tetrahedron*, **26**, 3619 (1970).

(19) Kindly supplied by Professor E. J. Corey.

(20) Several 11-substituted 11-deoxyprostaglandins have recently been obtained *via* the 1,4 addition to the methyl ester of PGA_2 obtained from marine sources [C. V. Grudzinskas and M. J. Weiss, *Tetrahedron Lett.*, 141 (1973)].

In addition, starting from compound **1** (X = alkyl, H), various C-11 alkylprostaglandins and C-11 deoxyprostaglandins have been synthesized. By varying the

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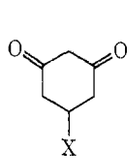
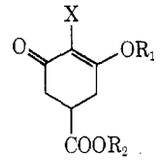
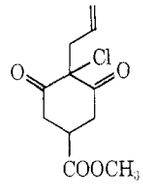


1, X = COOH



2, X = H; $R_1 = R_2 = CH_2CH{=}CH_2$
3, X = $R_2 = CH_2CH{=}CH_2$; R_1 = Ac
4, X = $CH_2CH{=}CH_2$; R_1 = H; $R_2 = CH_3$



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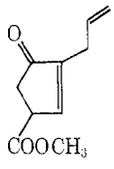

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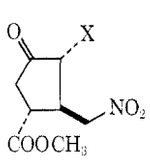
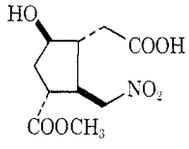


7, X = $CH_2CH{=}CH_2$
8, X = CH_2COOH



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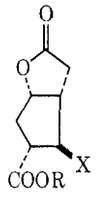
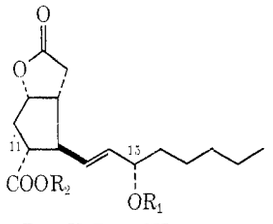
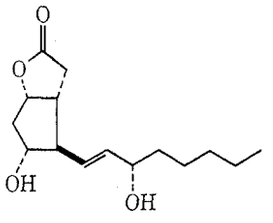


10, X = CH_2NO_2; R = CH_3
11, X = CH_2NO_2; R = H
12, X = CHO; R = CH_3
13, X = $CH{=}CHCO_nC_5H_{11}$; R = CH_3



14, R_1 = H; $R_2 = CH_3$
15, $R_1 = R_2$ = H
16, R_1 = Ac; R_2 = H
17, R_1 = Ac; $R_2 = OCOC_6H_4Cl$-*m*



18

type of Wittig reagent used, various side-chain analogs have also been prepared. Description of this work is in preparation.

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The Oxymercuration of *cis*- and *trans*-Di-*tert*-butylethylene. Evidence for a π-Bridged Intermediate

Summary: The methoxymercuration of *cis*-di-*tert*-butylethylene proceeds by an anti addition without molecular rearrangement or carbon–carbon bond rotation providing evidence for a π-bridged intermediate.

Sir: The intermediacy of mercurinium ions in the oxymercuration reaction has been the subject of recent controversy. Arguments for[1] and against[2] the involvement of these mercury-bridged π complexes have recently appeared in the literature. Although kinetic studies[3] have not yet provided evidence for mercurinium ions under oxymercurating conditions, they have been observed in solution[4] and in the gas phase.[5] We now report convincing evidence for significant π bridging in the oxymercuration of the highly strained *cis*-di-*tert*-butylethylene (**1**). Our results also clearly demonstrate that alkene strain energy is not a dominant factor in the rate of oxymercuration of alkenes.

On the basis of theoretical calculations[6] and photoelectron spectroscopy,[7] **1** has been determined to be essentially a planar alkene with relief of steric repulsions of the *tert*-butyl groups being manifested by in-plane angle distortion (C–C–*tert*-butyl bond angle, 136°). The ground-state energy of **1** is 10.2 kcal/mol[8] higher in energy than the relatively unstrained *trans*-di-*tert*-butylethylene (**2**). The difference in strain energy between **1** and **2** provides a unique opportunity to examine the question as to whether the steric repulsion between the *cis*-*tert*-butyl groups is sufficient to destabilize the π-bridged mercurinium ion by C_1–C_2 bond rotation affording a free carbonium ion.

Methoxymercuration of **1** with $Hg(ClO_4)_2$ in methanol solvent followed by Cl^- treatment afforded *dl*-*threo*-3-(chloromercuri)-4-methoxy-2,2,5,5-tetramethylhexane (**3**)[9] by the preferred anti addition[10] (eq 1). The structural assignment of **3** was based on the vicinal H_1–H_2 coupling constant[11] ($J_{H_1,_2}$ = 1.6 Hz) and on the nmr chemical-shift difference[12] of the methoxyl resonance in carbon tetrachloride and pyridine solvent. Methoxymercuration of **2** with $Hg(ClO_4)_2$ also afforded the threo isomer **3** by a syn addition to the double bond. This provides the first example of a syn addition to an unstrained alkene in the oxymercuration reaction and

(1) D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, **93**, 6902 (1971); R. D. Bach and R. F. Richter, *ibid.*, **94**, 4747 (1972), and references cited therein.
(2) H. C. Brown and K.-T. Liu, *J. Amer. Chem. Soc.*, **93**, 7335 (1971).
(3) J. Halpern and H. B. Tinker, *J. Amer. Chem Soc.*, **89**, 6427 (1967).
(4) G. H. Olah and P. R. Clifford, *J. Amer. Chem Soc.*, **93**, 1261, 2320 (1971).
(5) R. D. Bach, J. Gauglhofer, and L. Kevan, *J. Amer. Chem. Soc.*, **94**, 6860 (1972).
(6) N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, **94**, 5734 (1972); E. H. Weibenga and E. Bowhuis, *Tetrahedron*, **25**, 453 (1969).
(7) M. B. Robin, G. N. Taylor, N. H. Kuebler, and R. D. Bach, *J. Org. Chem.*, **38**, 1049 (1973).
(8) J. D. Rockenfeller and F. D. Rossini, *J. Phys. Chem.*, **65**, 267 (1961).
(9) The compound had mp 85.5–87°; ir (CCl_4) 1040 cm^{-1} (COC); nmr (CCl_4) 213.7 Hz (s, 3), δ 3.15 (d, 1, J = 1.6 Hz), 2.13 (d, 1, J = 1.6 Hz), 0.99 (s, 9).
(10) W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968).
(11) The *dl*-*dichloride* derived from anti addition of Cl_2 to **1** has a ^{13}C–H coupling constant of 0.8 Hz while the meso isomer has a coupling constant of 5.2 Hz: R. C. Fahey, *J. Amer. Chem. Soc.*, **88**, 4681 (1966).
(12) R. F. Richter, J. C. Philips, and R. D. Bach, *Tetrahedron Lett.*, 4327 (1972).