Liberal Arts, Osaka University), who kindly made the mass spectral data of our final product available.

Registry No. 11, 3958-79-0; (±)-12, 75534-45-1; (±)-13, 75534-46-2; (±)-14, 75534-47-3; (±)-16, 75534-48-4; (±)-17, 75534-49-5; (-)-17, 75597-71-6; (-)-17 cinchonidine salt, 75657-47-5; (+)-17, 75597-72-7; (+)-18, 75534-50-8; (-)-19, 75534-51-9; (-)-20, 75534-52-0; (-)-22, 75534-53-1; (+)-23, 75534-54-2; (+)-24, 75534-55-3; 25, 75534-56-4; (+)-26, 75534-57-5; 27, 75534-58-6; (-)-28, 75548-49-1; methyl 2,5-dihydroxybenzoate, 2150-46-1; cyclopentadiene, 542-92-7.

Intramolecular α-Amidoalkylation of an Olefin for the Synthesis of a Useful Prostaglandin Intermediate†

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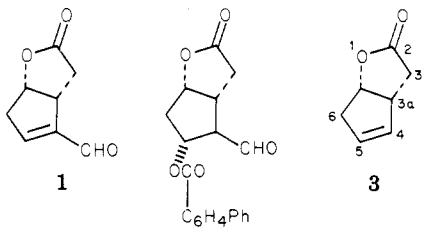
The α,β-unsaturated aldehyde 1 is an important intermediate in the preparation of a number of prostaglandins such as prostaglandin C_2 and thromboxane B_2. A method was developed by starting with the ene lactone 3 and using an intramolecular α-amidoalkylation reaction as the key step that made available this useful molecule in six operations. Formation of the lactam 15, as well as its final conversion to the target aldehyde 1, will be discussed.

The α,β-unsaturated aldehyde 1 is a tantalizing target for synthesis. To date, it has served as the key intermediate in the preparation of three different prostaglandin derivatives, namely, the 11,12-difluoromethano-prostaglandins,[1] prostaglandin C_2[2] and thromboxane B_2.[3] Substance 1 is available via the Corey intermediate 2 by



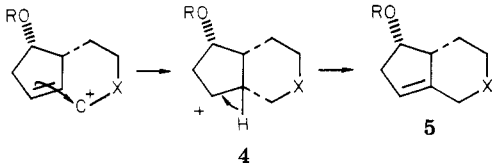
1 2 3

the base-promoted elimination of the C_{11} substituent, thus destroying two of the four meticulously constructed asymmetric centers. A search for an alternative and possibly more straightforward approach to 1 was therefore undertaken.

Discussion

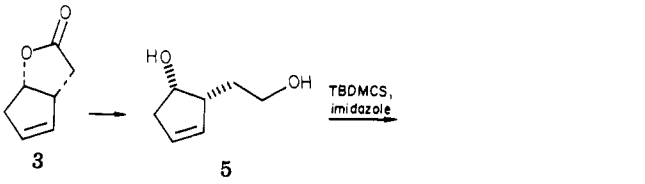
The commercially available ene lactone 3 has been prepared in optically active form.[4] It already possesses both the asymmetric centers of 1 and is obviously an attractive starting material. The problem at hand is therefore the regiospecific introduction of a carbon atom at one end of the double bond, namely, C_4. We considered a strategy involving the delivery of a carbonium ion by the two-carbon side chain on the cyclopentene ring to effect an electrophilic attack on the unsaturated center.

Loss of a proton from the more substituted carbon in the initial intermediate 4 (eq 1) would lead to the bicyclic olefin 5, where X = O or N, and conversion of the latter into the desired aldehyde 1 should be achievable by standard synthetic methodology.



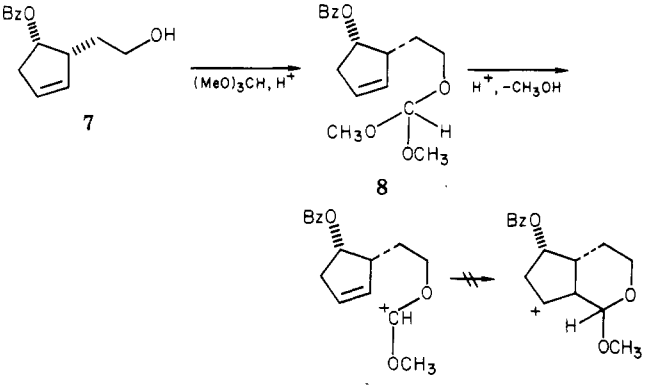
4 5 (1)

Scheme I



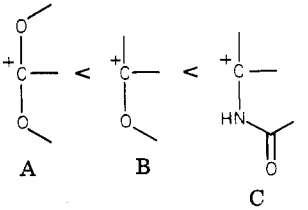
3 5 6 7

Scheme II



7 8 8a

Three types of carbonium ions with increasing reactivity were studied: the doubly stabilized A, the singly stabilized B, and the α-amido carbonium ion C.



A B C

† Contribution No. 570.

(1) P. Crabbe and A. Cervantes, *Tetrahedron Lett.*, 1319 (1973).
(2) R. C. Kelly, I. Schletter, and R. L. Jones, *Prostaglandins*, 4(5), 653 (1973).
(3) N. A. Nelson and R. W. Jackson, *Tetrahedron Lett.*, 3275 (1976).
(4) J. J. Partridge, N. K. Chadha, and M. R. Uskokovic, *J. Am. Chem. Soc.*, 98, 7171 (1973).

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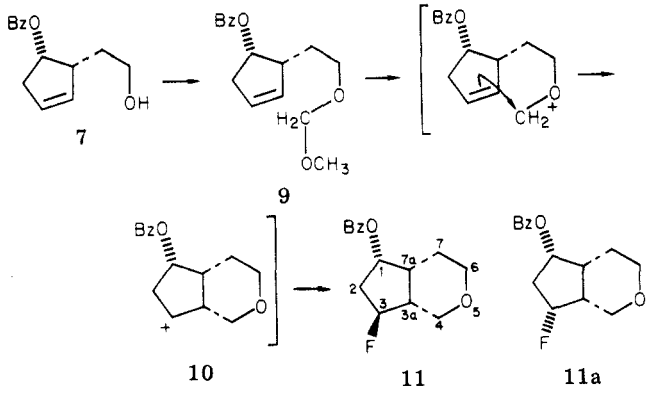
Scheme III



Results

Selective protection of the primary alcohol of diol **5** as the *tert*-butyldimethylsilyl ether **6**[5] was achieved (Scheme I). Benzoylation of the secondary alcohol followed by acid-induced cleavage of the silyl ether gave the desired monobenzoate **7**.

Treatment of alcohol **7** in trimethyl orthoformate in the presence of an acid catalyst gave a mixed orthoformate (**8**, Scheme II), but we were unable to bring about the desired attack on the double bond even under forcing conditions. Presumably the doubly stabilized carbonium ion **8a** is insufficiently reactive to add to the rather inert cyclopentenyl double bond.[6]

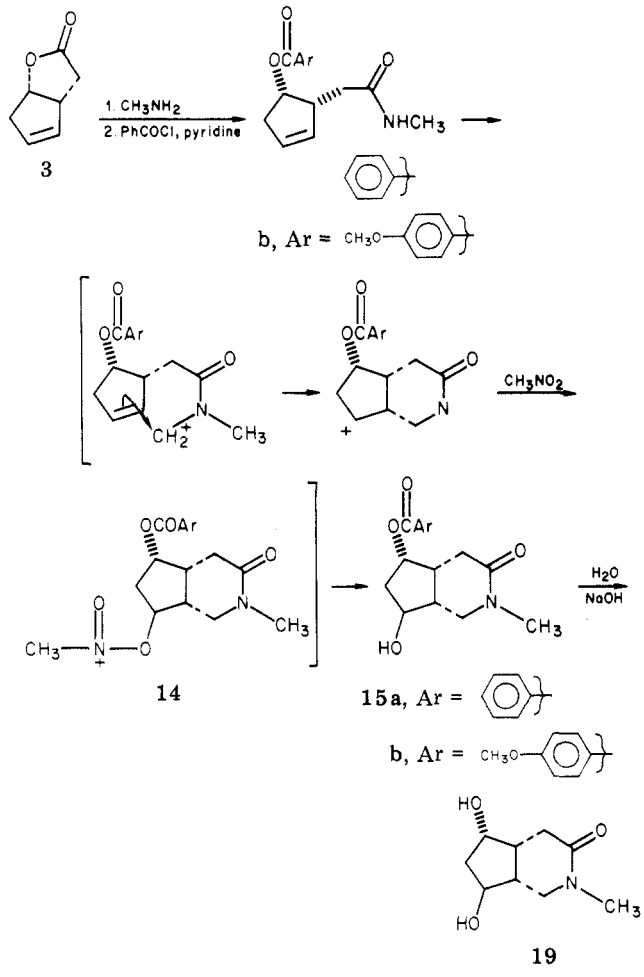
When the monobenzoate alcohol **7** was treated with acid in methylal, a mixed acetal (**9**) was obtained (Scheme III). Further treatment of the mixed acetal with boron trifluoride in methylal resulted in the expected intramolecular electrophilic addition to the olefinic bond. However, the anticipated intermediate carbonium ion (**10**) failed to eliminate a neighboring proton but captured a nucleophile and gave the fluoro compounds **11** and **11a**.[7]

Abstraction of a hydride from the acetal methylene of compound **9** would be an alternate source of the carbonium ion **8a**. Reaction of trityl fluoroborate with acetal **9** gave, unexpectedly, the same cyclization product (**11**), as well as its isomer (**11a**).

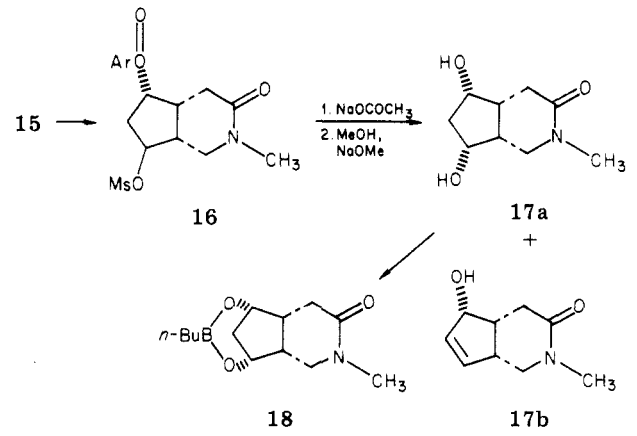
Amide **13** was prepared by reaction of the lactone **3** with monomethylamine to give the hydroxyamide **12** which without purification was treated with benzoyl chloride in pyridine to furnish the crystalline amide ester **13** in 76% overall yield (Scheme IV).

Intramolecular α-amidoalkylation[8] was carried out on the amide **13** with paraformaldehyde in nitromethane as solvent and trifluoroacetic acid as the catalyst, giving the lactam **15** in 57% yield. Presumably a solvent molecule participated to provide the nitronate ester **14** which was hydrolyzed during workup. In a parallel set of experiments the *p*-anisoate **13b** was obtained, which after being subjected to α-amidoalkylation reaction conditions gave the lactam **15b**. The mesylate **16** was prepared from the hydroxy lactam **15b** and was treated with sodium acetate in the presence of dibenzo-18-crown-6.[9] The major product

Scheme IV



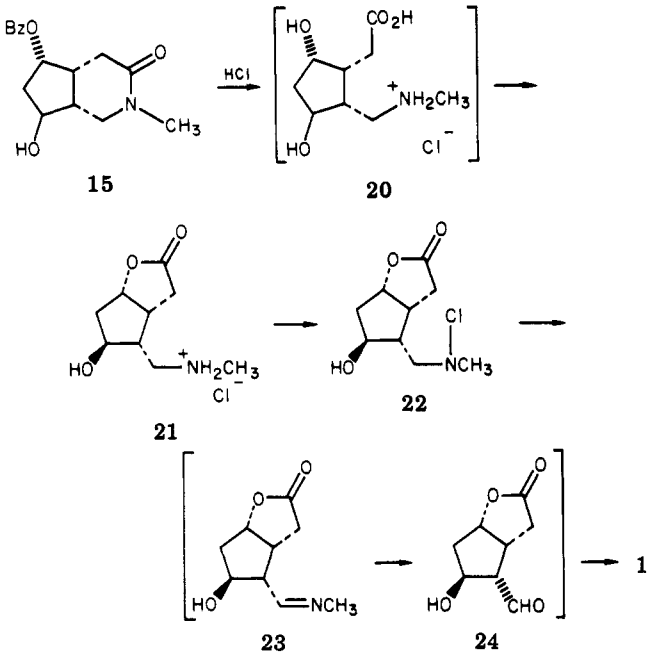
Scheme V



was an olefin, the result of elimination of the mesylate which was hydrolyzed to the alcohol **17b** (Scheme V). The only other discernible product gave, after base-promoted hydrolysis, a diol (**17**) which formed a cyclic *n*-butyl boronate ester (**18**) evident through observation of its molecular ion in the mass spectrum. When the benzoate of lactam **15b** was hydrolyzed with base, the resulting diol (**19**) failed to form a cyclic boronate ester under identical conditions. These results indicated that the stereochemistry of the free hydroxyl group in latam **15** is trans to the

(5) K. K. Ogilvie and D. J. Iwacha, *Tetrahedron Lett.*, 317 (1973).
(6) See, for example, J. W. Copenhaver, U.S. Patent 2677708 (1954).
(7) This reaction is related to the Prins reaction. A recent publication describes an elegant application of the Prins reaction in the synthesis of similar molecules where the regioselectivity was kinetically imparted: I. Tomoskozi, L. Gruber, G. Kovacs, I. Szekely, and V. Simonidesz, *Tetrahedron Lett.*, 4639 (1976).
(8) H. E. Zaugg, *Synthesis*, 49 (1970); W. D. Schaeffer, U.S. Patent 3190882 (1965); O. O. Orazi and R. A. Corral, *J. Chem. Soc., Chem. Commun.*, 470 (1976).
(9) C. J. Peterson, *J. Am. Chem. Soc.*, **89**, 7017 (1967); *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972).

Scheme VI



benzoate group. On thermodynamic grounds the cis fusion is favored in bicyclic compound **15a**, and spectral data support this assignment.[10] Heating the lactam **15a** in 15% aqueous hydrochloric acid caused the hydrolysis of both the lactam and the benzoate ester, and the resulting hydroxy acid (**20**) cyclized under the reaction conditions to give lactone **21** isolated as the hydrochloride salt in 92% yield (Scheme VI). Chlorination of the corresponding free amine with *tert*-butyl hypochlorite[11] furnished the *N*-chloro derivative **22** in 83.5% yield, and treatment of the latter with sodium methoxide followed by an aqueous acid workup gave the desired enealdehyde (**1**) via the unstable intermediate imine **23** and hydroxy aldehyde **24**.

The best overall yield achieved for the conversion of *N*-chloro amine **22** to the final ene aldehyde **1** was 41%. Alternately, the target molecule (**1**) could be obtained directly from the hydrochloride salt **21** without isolation of the *N*-chloro amine (**22**). Thus, by carrying out N-chlorination in the presence of excess sodium methoxide followed by the aqueous acid workup as before, the ene aldehyde **1** was obtained in an overall yield comparable to that achieved in the stepwise procedure.

We have demonstrated the feasibility of our original concept. By use of intramolecular delivery, a carbon atom has been introduced regiospecifically into olefin **3**. Thus, starting with ene lactone **3**, via intermediates **13**, **15**, and **21**, the ene aldehyde **1** is available in five operations, in 14% overall yield.

Experimental Section

Preparation of 1-(Benzoyloxy)-2-(2-hydroxyethyl)cyclopent-3-ene (7). A 25-mL, round-bottomed flask with a magnetic stirrer and N_2 atmosphere was charged with 1-hydroxy-2-(2-hydroxyethyl)cyclopent-3-ene (**5**; 4.38 g, 34.52 mmol), imidazole (6.3 g, 85.6 mmol), and DMF (8.8 mL). The mixture was stirred until homogeneous and then cooled in an ice bath, and chloro-*tert*-butyldimethylsilane (5.17 g, 34.2 mmol) was added. Stirring was continued for 3 h at 0 °C.

The reaction mixture was poured into water and extracted with ether. The organic phase was dried with $MgSO_4$, and most of the solvent was removed on a rotary evaporator. The crude liquid product (**6**) was used directly in the next reaction (GC analysis (6-ft column, 3% SE-30) indicated that this sample was contaminated with roughly 2% of the disilyl ether): IR (film) 3350 (br), 1250 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 0.95 (s, 9, *t*-Bu), 3.76 (t, 2, J = 6 Hz, OCH_2), 4.42 (m, 1, OCH), 5.65 (m, 2, HC=CH).

The crude monosilyl ether **6** was put in a round-bottomed flask with magnetic stirrer and N_2 atmosphere, and dry pyridine (12 mL) and benzoyl chloride (7.5 g, 51.5 mmol, 6.2 mL) were added. The reaction was stirred at room temperature overnight and could be followed by TLC (silica gel; 1:4 acetone/hexane).

The reaction mixture was poured into water and extracted with ether several times. The combined organic phases were washed with aqueous $NaHCO_3$, water, 10% aqueous HCl, water, and brine and then dried over $MgSO_4$. After removal of the solvent, the crude product was chromatographed on silical gel by eluting with 1:9 acetone/hexane. This liquid material was used directly for the hydrolysis: IR (film) 1720, 1250 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 0.85 (s, 9, *t*-Bu), 3.70 (t, 2, J = 6.5 Hz, OCH_2), 5.7 (m, 3, HC=CH and CHO), 7.5 (m, 3), 8.0 (m, 2, arom).

The monosilyl ether monobenzoate from the previous reaction was placed in a round-bottomed flask with 20 mL of water, 160 mL of THF, and 4 drops of concentrated HCl and stirred at room temperature for 2 days, or until TLC (3:7 EtOAc/hexane) showed no more starting material present.

The reaction was made basic with solid $NaHCO_3$, and then most of the THF was removed under reduced pressure. Ether was added, and the solution was washed with water and brine. The solvent was evaporated, and the product was purified by chromatography on silica gel (500 g; gradient elution from 10% EtOAc in hexane to 40% EtOAc in hexane): yield 3.54 g of monobenzoate **7**; colorless liquid (44.5% overall yield from the diol **5**; IR (film) 3300, 1705, 1270, 710 cm^{-1}; NMR (60 MHz, $CDCl_3$) 3.75 (t, 2, J = 6.5 Hz, CH_2O), 5.7 (m, 3, CF=CH and CHO), 7.5 (m, 3), 8.0 (m, 2, arom). Anal. Calcd for $C_{14}H_{16}O_3$: mol wt 232.27; C, 72.39; H, 6.94; O, 20.67. Found: C, 72.56; H, 6.98.

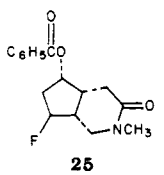
Preparation of 1-(Benzoyloxy)-2-[2-(dimethoxymethoxy)ethyl]cyclopent-3-ene (8). The hydroxy ester **7** (0.977 g, 4.2 mmol), trimethyl orthoformate (20 mL), anhydrous Dowex-50 resin, and Linde 4-Å molecular sieves were stirred together in a round-bottomed flask under N_2. The reaction was slightly exothermic, and after 30 min according to TLC analysis (silica, 3:7 EtOAc/hexane) it was complete.

The solution was filtered through Celite filter aid, and the excess trimethyl orthoformate and methanol were removed under reduced pressure. The yield of the colorless liquid was 1.26 g (97.5%, 4.1 mmole): IR (film) 2900, 1710, 1270 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 3.30 (s, 6, OCH_3), 3.65 (t, 2, J = 6.5 Hz, CH_2O), 5.00 (s, 1, OCH), 5.70 (m, 3, CH=CH and CHO), 7.50 (m, 3), 8.0 (m, 2, arom).

Preparation of 1-(Benzoyloxy)-2-[2-(methoxymethoxy)ethyl]cyclopent-3-ene (9). A round-bottomed flask with a reflux condenser and a magnetic stirrer and under a nitrogen atmosphere was charged with the hydroxy ester **7** (450 mg, 1.95 mmol), dimethoxymethane (20 mL, purified by distillation from sodium), Linde 4-Å molecular sieves (10 cm^3), and a catalytic amount of anhydrous Dowex-50 acid resin. The mixture was heated to reflux for 24 h until TLC analysis (silica, EtOAc/hexane) indicated that the exchange was complete.

The solids were removed by filtration through Celite, and the filtrate was concentrated under reduced pressure to give essentially a quantitative yield of the pure mixed acetal as a colorless liquid:

(10) With boron trifluoride as catalyst, the product of intramolecular α-amidoalkylation is the lactam **25**, whose stereochemistry was assigned by ^{13}C NMR comparison with a series of C_{11}-fluoro prostaglandin derivatives prepared in this Institute. Comparison of the ^{13}C NMR spectrum of lactam **15** with that of **25** furnishes independent support for the assignment of cis ring fusion stereochemistry to the former. We are grateful to Dr. M. Maddox for these studies.



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(11) H. Ruschig, *Med. Chem.* (*Leverkusen, Ger.*), 4, 327 (1942); W. E. Bachmann, M. P. Cava, and A. S. Dreiding, *J. Am. Soc.*, 76, 5554 (1954); M. P. Cava and B. R. Vogt, *Tetrahedron Lett.*, 2813 (1964).

NMR (100 MHz, $CDCl_3$) δ 3.30 (s, 3, OCH_3), 3.61 (t, 2, J = 6.5 Hz, CH_2O), 4.70 (s, 2, OCH_2O), 5.70 (m, 3, HC=CH and CHO), 7.45 (m, 3), 8.0 (m, 2, arom). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.60; H, 7.49.

Cyclization Experiments of 1-(Benzoyloxy)-2-(2-(methoxymethoxy)ethyl)cyclopent-3-ene (9). Experiment A. A stock solution of trityl fluoroborate (1 g) in 20 cm^3 of methylene chloride was prepared. To a dried flash charged with 5.8 cm^3 of the trityl fluoroborate solution and a magnetic stirring bar was added 240 mg of the acetal **9**. The solution was stirred under a nitrogen atmosphere for 2 days. Progress of the reaction was monitored by TLC (30% ethyl acetate in hexane, silica gel GF). The reaction mixture was partitioned between ether and water. The ethereal solution was washed with $NaHCO_3$ solution and brine, dried over magnesium sulfate, and evaporated to give a glassy material. Chromatography on a silica gel column using 10% ethyl acetate in hexane gave a liquid fraction (62 mg) which was assigned the structure **11**: IR (film) 1710, 1265, 1156, 1075, 1050, 1025 cm^{-1}; ^{19}F NMR δ 178 (m); ^{13}C NMR δ 75.24 (C_1, J_F = 4.0 Hz), 36.46 (C_2, $J_{2\text{-}F}$ = 22.80 Hz), 92.88 (C_3, $J_{3\text{-}F}$ = 178 Hz), 43.90 (C_{3a}, $J_{3a\text{-}F}$ 11.3 Hz), 66.12 (C_4), 65.99 (C_6), 23.11 (C_7), 38.44 (C_{7a}, $J_{7a\text{-}F}$ = 5 Hz); ^1H NMR δ 5.3 (H_3, $J_{3\text{-}F}$ = 50 Hz); mass spectrum, m/e 264 (M^+), 159 (M^+ - 105), 142 (M^+ - benzoic acid), 105 ($PhC{\equiv}O^+$). A second liquid fraction was collected (46 mg) and assigned the structure **11a**: IR (film) 1720, 1265, 1115, 1070, 1050, 1025 cm^{-1}; ^{19}F NMR δ 177.0 (m); ^{13}C NMR δ 75.47 (C_1, $J_{1\text{-}F}$ = 2.21 Hz), 38.69 (C_2, ($J_{2\text{-}F}$ = 24.26 Hz), 94.7 (C_3, $J_{3\text{-}F}$ = 182.37 Hz), 40.65 (C_{3a}, ($J_{3a\text{-}F}$ = 19.12 Hz), 64.82 (C_4, $J_{4\text{-}F}$ = 7.35 Hz), 66.03 (C_6), 23.28 (C_7), 38.17 (C_{7a}); ^1H NMR δ 5.1 (H_3, $J_{3\text{-}f}$ = 50 Hz); mass spectrum, m/e 264 (M^+), 159 (M^+ - 105), 142 (M^+ - benzoic acid), 105 ($PhC{\equiv}O^+$).

Experiment B. A solution of 12 mg of the acetal **9** in 1 mL of methylene chloride was treated with 1 drop of boron trifluoride etherate. The solution was stirred at room temperature overnight and then poured into sodium bicarbonate solution. The product was extracted with methylene chloride. Thin-layer chromatography (silica gel GF, 30% ethyl acetate in hexane) as well as gas chromatography (6-ft column, 3% SE-30, oven temperature 170 °C) indicated that the product mixture consists of three components, the alcohol **7**, isomer **11**, and isomer **11a**.

Preparation of 1-(Benzoyloxy)-2-[(*N*-methylcarbamoyl)methyl]cyclopent-3-ene (13a) and 1-(Anisoyloxy)-2-[(*N*-methylcarbamoyl)methyl]cyclopent-3-ene (13b). A solution of the lactone **3** (1.50 g) in 25 mL of benzene was placed in a flask equipped with a gas-inlet tube extending below the surface of the solution. A slow steady stream of methylamine was bubbled through the solution. The progress of the reaction was monitored by thin-layer chromatography (silica gel GF, 1/1 acetone/hexane). After 24 h the reaction was complete. The mixture was evaporated under vacuum on a Büchi rotary evaporator without heating. To the crude hydroxy amide in a solution of 6 mL of pyridine and 20 mL of benzene was added dropwise 3.37 g of benzoyl chloride in 3 mL of benzene. Stirring was continued at room temperature for 1.5 h, and the reaction mixture was added dropwise to a rapidly stirred solution of 10 mL of saturated sodium bicarbonate solution in 40 mL of water. Ether extraction was followed by washes with concentrated sodium bicarbonate solution, 10% hydrochloric acid, and brine. The ether layer was dried over magnesium sulfate and evaporated to give a yellow oil. The product was dissolved in 150 mL of hot cyclohexane and upon cooling yielded 2.04 g of white crystals. A second crop of 335 mg of crystals could be obtained from the mother liquor (yield 76% of **13a**). Recrystallization from benzene–hexane gave the analytical sample: mp 95–96 °C; IR (CH_2Cl_2) 3470, 1720, 1675 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 2.70 (d, 3, J = 5 Hz, NCH_3), 3.44 (br q, 1, J= 8 Hz, C_2H), 5.65 (m, 1, CH), 5.70 (s, 2, C_3H and $C_{4\text{-}H}$); mass spectrum, m/e 259 (M^+). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.50; H, 6.71; N, 5.13.

When the crude hydroxy amide was treated with anisoyl chloride in pyridine, 1-(anisyloxy)-2-[*N*-(methylcarbamoyl)-methyl]cyclopent-3-ene (**13b**) was obtained; mp 101–103 °C. Anal. Calcd for $C_{16}H_{19}NO_4$: mol wt 289.32; C, 66.42; H, 6.62; N, 4.84. Found: C, 66.37; H, 6.42; N, 4.66.

Cyclization via Intramolecular α-Amidoalkylation of Olefin; Preparation of Lactams 15a and 15b. A mixture of 0.80 g of paraformaldehyde in 60 mL of trifluoroacetic acid and 200 mL of nitromethane was stirred at room temperature for 30 min. The solution became homogeneous, and then 4.00 g of the ester amide **13** was added. After 3 days an additional 200 mg of paraformaldehyde was added and stirring continued overnight. The reaction mixture was evaporated on a Büchi Rotovap. The residue was dissolved in methylene chloride, added to 150 mL of water, and carefully neutralized with potassium carbonate. The layers were separated, and the organic layer was washed with 1 N K_2CO_3 solution and brine, dried over sodium sulfate, and evaporated to yield 5.6 g of brown oil. This material was chromatographed on 300 g of silica gel with 50:50 acetone/hexane and pure acetone with gradient elution. The fraction containing the product weighed 3.0 g, which yielded 1.75 g of crystals on recrystallization from acetone. A second crop of 780 mg was collected from the mother liquor. The total yield of **15a** was 2.53 g (57%). The analytical sample melted at 107–110 °C: IR (CH_2Cl_2) 3640, 1720, 1660, 110 cm^{-1}; ^1H NMR δ 2.95 (s, 3, NCH_3), 3.35 (m, 2, CH_2N), 4.14 (q, 1, J = 6 Hz, CHOH), 5.46 (br q, 1, J = 4.5 Hz, CHOCOPh); ^{13}C NMR δ 30.82 (C_6), 35.08 (C_{NCH_3}), 38.07 (C_{7a}), 40.83 (C_2), 44.99 (C_{3a}), 49.80 (C_4), 73.76 (C_3), 76.20 (C_1), 166.16 (C_6); mass spectrum, m/e 289 (M^+), 184, 110, 105. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.21; H, 6.64; N, 4.88.

When the anisoate **13b** was used as the starting material in the cyclization reaction, the corresponding lactam, **15b**, was obtained in 60% yield as a viscous oil: ^1H NMR δ 2.95 (s, 3, NCH_3), 3.40 (m, 2, CH_2N), 3.82 (s, 3, OCH_3), 4.20 (q, 1, J = 6 Hz, CHOH), 5.52 (br, 1, CHOCOAr); ^{13}C NMR δ 30.87 (C_6), 35.08 (C_{NCH_3}), 38.10 (C_{7a}), 40.96 (C_2), 45.09 (C_{3a}) 49.84 (C_4), 55.50 ($COCH_3$), 73.88 (C_3), 75.82 (C_1), 165.89 (C_6); mass spectrum, m/e 319 (M^+), 184, 167, 135.

Assignment of Stereochemistry of Isomeric Diols 17 and 19; Formation of a Cyclic Boronate Ester. A solution of 50 mg of the lactam anisoate **15b** in 0.422 mL of a 0.372 M solution of sodium methoxide in methanol was stirred at room temperature for 18 h. The reaction mixture was acidified with hydrochloric acid and evaporated to dryness. Methyl anisoate was removed by ether extraction and the residual diol (**19**) was derivatized with *N,N*-bis(trimethylsilyl)trifluoroacetamide and 1% trimethylchlorosilane: mass spectrum, m/e (M^+), 314 (M^+ - CH_3), 239, 149, 110 (base peak). Treatment of diol **19** with *n*-butylboronic acid followed by BSTFA and 1% Me_3ClSi did not give a peak in the gas chromatograph/mass spectrum with M^+ at m/e 251, corresponding to the cyclic boronate ester.

Methanesulfonyl chloride 60 mg was added to a solution of the lactam **15b** (140 mg) and triethylamine (90 mg) in 10 mL of methylene chloride cooled to −20 °C with a dry ice–acetone bath. After 45 min the reaction mixture was poured into water. The organic solution was washed with water, dried over magnesium sulfate, and evaporated to give 170 mg of a viscous oil (**16**): IR (film) 1700, 1660, 1600, 1500, 1350, 1260, 1170 cm^{-1}; ^1H NMR δ 3.00 (s, 6, NCH_3 and SO_2CH_3), 3.46 (dd, 2, J = 5 Hz, CH_2N---), 3.81 (s, 3, OCH_3), 5.00 (m, 1, CH(OMs)), 5.50 (m, 1, CHOC).

A crude sample of **16** (160 mg) was treated with 330 mg of sodium acetate in 10 mL of dimethylformamide in the presence of 250 mg of dibenzo-18-crown-6 at 90 °C overnight. The solvent was removed under vacuum, and the organic material was picked up with ether and separated by column chromatography (15 g of silica gel, 1% methanol in methylene chloride).

The major fraction was treated with a 0.372 M solution of sodium methoxide in methanol for 20 h at room temperature. After removal of the solvent, the alcohol **17b** was purified by thick-layer chromatography (silica gel, 1:1 acetone/hexane): ^1H NMR δ 2.88 (s, 3, NCH_3), 4.85 (br d, 1, CH(OH)), 5.8 (AB q, 2, J = 21, 6 Hz, CH=CH); mass spectrum, m/e 167 (M^+), 149 (M^+ - H_2O).

The minor fraction was hydrolyzed under identical conditions to give the diol **17a**: mass spectrum (derivatized with BSTFA and 1% Me_3ClSi), m/e 329 (M^+), 314 (M^+ - CH_3), 239 (M^+ - Me_3SiOH), 149 (M^+ - 2 Me_3SiOH), 110 (base peak).

The diol **17a** was treated with *n*-butylboronic acid; mass spectrum, m/e 251 (M^+), 236, 222, 209, 194, 110 (base peak).

Hydrolysis of Lactam 15a. A sample of 3.90 g (13.5 mmol) of lactam **15a** was mixed with 100 mL of 15% hydrochloric acid and heated to 90 °C for 20 h. The solution was then cooled to

0 °C with an ice bath, and crystals of benzoic acid precipitated. The solid material was removed by filtration, and the filtrate was evaporated to dryness under vacuum. The residue was treated with 60 mL of acetone overnight, and the hygroscopic amine salt **21** solidified, collected by filtration, and washed with acetone. The yield of the white solid was 2.754 g (12.46 mmol, 92%): mp 150–151.5 °C; IR (Nujol) 3330, 2420, 1770, 1600 cm^{-1}; ^1H NMR (D_2O) δ 2.80 (s, 3, NCH_3), 4.20 (m, 1, CHOH), 5.25 (m, 1, CHOO); ^{13}C NMR δ 179.22 (C_2), 84.26 (C_{6a}), 73.80 (C_5), 42.07 (C_{3a}), 39.63, (C_6), 36.87 (C_3); mass spectrum, m/e 185 (M^+), 110, 44.

Conversion of the Lactone Amine Hydrochloride 21 into the Ene Aldehyde 1. A 50-mL, round-bottomed flask under nitrogen atmosphere was charged with the amine salt (1.0 g, 4.5 mmol) and 30 mL of methanol. Once the salt had dissolved, *tert*-butyl hypochlorite (550 mg, 9.2 mmol) was added, followed by solid sodium bicarbonate (375 mg, 4.46 mmol). After the mixture was stirred at room temperature for 1.5 h the solvent was removed under vacuum, and the product was isolated by chromatography on 100 g of silica gel (eluted with 3:7 acetone/hexane) to give **22** as a clear oil: 824 mg (3.76 mmol, 83.5% yield); IR (film) 3350, 2900, 1760, cm^{-1}; ^1H NMR δ 2.98 (s, 3, NCH_3), 4.07 (m, 1, CHOH), 5.04 (t, 1, CHOC).

To a solution of the *N*-chloro amine (825 mg, 3.77 mmol) in 20 mL of anhydrous ether was added a solution of sodium methoxide, made by solution of sodium (172 mg, 7.48 mmol) in 4 mL of methanol. There was an immediate precipitate, and the stirring was continued for 30 min at room temperature. An equal volume of 30% aqueous sulfuric acid was added, and the heterogeneous mixture was stirred overnight. The layers were separated, and the aqueous layer was extracted exhaustively with methylene chloride. The combined organic fractions were dried over sodium sulfate and evaporated to give the solid aldehyde **1** (234 mg, 1.54 mmol, 41%). Chromatography on silica gel (eluted with 40% acetone in hexane) gave the analytically pure sample: mp 49–51.5 °C; IR (CH_2Cl_2) 3700, 3050, 2740, 2840, 1780, 1680, 1170 cm^{-1}; ^1H NMR δ 2.75 (m, 2, CH_2CO), 2.95 (m, 2, $CH_2C{=}C$), 3.72 (br, 1, $CHC{=}C$), 5.21 (m, 1, CHOC), 6.89 (q, 1, $CH{=}$), 9.82 (s, 1, CHO); mass spectrum, m/e 152 (M^+), 124, 95, 79, 67. Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30; O, 31.55. Found: C, 63.39; H, 5.40.

This sample was compared with an authentic sample prepared according to the Corey route by thin-layer chromatography on silica gel (10% methanol in methylene chloride) as well as gas chromatography (6-ft column, 30% SE-30).

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Registry No. **1**, 75331-66-7; **3**, 26054-46-6; **5**, 75331-67-8; **5** disilyl ether, 75283-62-4; **6**, 75283-63-5; **6** benzoate, 75283-64-6; **7**, 75283-65-7; **8**, 75283-66-8; **9**, 75299-08-0; **11**, 75283-67-9; **11a**, 75331-68-9; **12**, 75283-68-0; **13a**, 75283-69-1; **13b**, 75283-70-4; **15a**, 75283-71-5; **15b**, 75283-72-6; **16**, 75283-73-7; **17a**, 75283-74-8; **17b**, 75283-75-9; **18**, 75283-76-0; **19**, 75331-69-0; **19** disilyl ether, 75363-08-5; **21**, 75283-77-1; **22**, 75283-78-2; chloro-*tert*-butyldimethylsilane, 18162-48-6; benzoyl chloride, 98-88-4; trimethyl orthoformate, 149-73-5; dimethoxymethane, 109-87-5; methylamine, 74-89-5; anisoyl chloride, 100-07-2; paraformaldehyde, 50-00-0; *n*-butylboronic acid, 4426-47-5; **17a** disilyl ether, 75283-79-3.

An Approach to the Synthesis of Unsymmetrically Substituted Chlorobiphenyls

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The Diels–Alder cycloaddition of *o*-chloranil with phenylacetylenes substituted with chlorine in the aryl ring can afford chlorobiphenyls upon photodecomposition of the bridged diketone adduct. Biphenyls derived from 3-chloro-, 4-chloro-, 2,4-dichloro-, and (2,5-dichlorophenyl)acetylene have been prepared by this route. These (chlorophenyl)acetylenes are available from the corresponding acetophenones. The applicability of this route suggests a general route to a number of biphenyls with 4–8 chlorines, which are not readily available by traditional biphenyl synthetic approaches. A further interest is the potential applicability of the route in providing specific homologues important in understanding the metabolic toxicology of chlorobiphenyls as a function of the distribution and number of chlorines present.

A central issue relating to the twin problems of chloro- and bromobiphenyls is to understand toxicological manifestations at the molecular level. Since toxicity varies with the number and pattern of halogen substitution, such understanding requires the use of pure compounds of diverse structural patterns, representing the 210 members each of the halobiphenyl series $C_{12}H_mX_n$ (m = 1 to 10, n = 10 − m). Very little work has been done in the bromo series. Except for some compounds in the chlorobiphenyl series which possess symmetry in substitution patterns in the two rings, studies have largely involved commercial mixtures or certain selected pure isomers.[1]

The synthesis of some of the symmetric chlorobiphenyl isomers is straightforward.[2] Approaches to unsymmetrically substituted analogues have not been widely pursued. Work described here illustrates the synthesis of five unsymmetrical congeners preparable unambiguously and in good yields without the presence of coproducts as impurities.

The method involves the photodecomposition of the Diels–Alder adduct **1**, formed from a (chlorophenyl)-acetylene and *o*-chloranil.[3] The preparation of dione adducts was accomplished by heating the appropriate chloro-substituted phenylacetylenes and *o*-chloranil at reflux in benzene solution for 12 h. Successful reactions were accomplished with (4-chlorophenyl)acetylene, (3-

(1) Conference Proceedings, National Conference on Polychlorinated Biphenyls, 1975 (published 1976), Environmental Protection Agency, Washington, DC, EPA 560/6-75-004; e.g., James D. McKinney "Toxicology of Selected Symmetrical Hexachlorobiphenyl Isomers: Correlating Biological Effects with Chemical Structure", pp 73–75. See also numerous contributions from "Health Effects of Halogenated Aromatic Hydrocarbons", W. J. Nicholson and J. A. Moore, Eds., *Ann. N.Y. Acad. Sci.* **320**, 0000 (1979).

(2) O. Hutzinger, S. Safe and V. Zitko, "The Chemistry of the PCB's", CRC Press, Cleveland, OH, 1974, Chapter 3, pp 41–71.

(3) (a) L. Horner and H. Merz, *Justus Liebigs Ann. Chem.*, **7**, 570 (1950); (b) J. L. Pyle, R. A. Lunsford, and J. S. Cantrell, *J. Org. Chem.*, **44**, 2391 (1979).

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