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Pyrrole Annulation onto Aldehydes and Ketones via Palladium-Catalyzed Reactions

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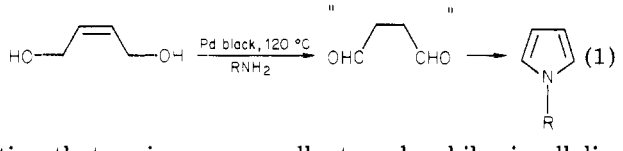
α-Dicarbonyl systems reacted with vinylmagnesium bromide and acetic anhydride to give α-acetoxy-α-vinylalkanones. These substrates react with benzylamine in the presence of tetrakis(triphenylphosphine)palladium to give *N*-benzylpyrroles with substituents in the two and/or three position. The functiodifferentiated synthesis of α-dicarbonyl compounds from ketones makes this a pyrrole annulation onto any α-methylene carbonyl system.

The recent development of synthetic methods for formation of α-diketones,[1-3] especially from aldehydes and ketones,[1,2] suggested their availability as basic building blocks for heterocycles. We developed a regiocontrolled approach to pyrroles which combines a functiodifferentiated synthesis of α-diketones with allylic alkylation catalyzed by palladium(0) complexes.

Pyrroles represent an important major class of heterocycles.[4] Their prominent place leads to continuing evolution of new synthetic methods. Most methods involve the use of 1,4-dicarbonyl systems. A most interesting varient is the in situ generation of the equivalent of such a system from (*Z*)-2-butene-1,4-diol (eq 1).[5] The observation that amines are excellent nucleophiles in allylic alkylation catalyzed by palladium(0) complexes[6] and the ready availability of 1,2-dicarbonyl systems[1-3] suggested a potentially very mild and flexible approach to pyrroles as outlined in eq 2.



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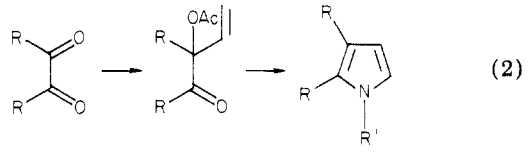

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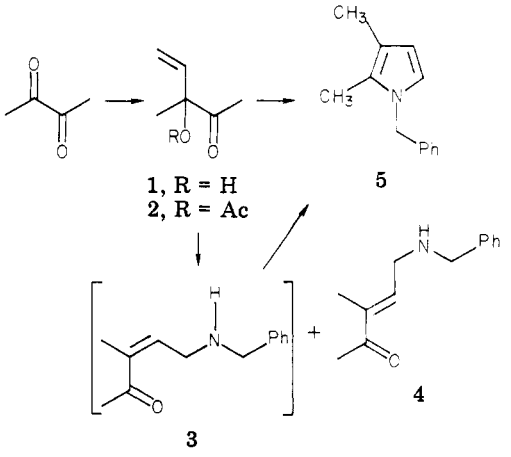
Treatment of biacetyl with vinylmagnesium bromide led to the monoaddition product 1 with no evidence for any diaddition adducts. Acetylation proceeded smoothly in the presence of 4-(dimethylamino)pyridine (DMAP) to give



(1) (a) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405. (b) Russell, G. A.; Hamprecht, G. *J. Org. Chem.* **1970**, *35*, 3007. (c) Thompson, J. E. *J. Org. Chem.* **1967**, *32*, 3947. (d) Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *J. Org. Chem.* **1971**, *36*, 1137. (e) Trost, B. M.; Salzmann, T. N. *J. Org. Chem.* **1975**, *40*, 148. (f) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (g) Yee, Y. K.; Schultz, A. G. *J. Org. Chem.* **1979**, *44*, 719. (h) Nagao, Y.; Kaneko, K.; Kawabata, K.; Fujita, E. *Tetrahedron Lett.* **1978**, 5021.

(2) Bauer, D. P.; Macomber, R. S. *J. Org. Chem.* **1975**, *40*, 1990. Mukaiyama, T.; Atsumi, K.; Takeda, T. *Chem. Lett.* **1975**, 1033. Wasserman, H. H.; Ives, J. L. *J. Am. Chem Soc.* **1976**, *98*, 7868. Takeda, T.; Ueda, M.; Mukaiyama, T. *Chem. Lett.* **1977**, 245.

(3) (a) Sharpless, K. B.; Lauer, R. F.; Repic, O.; Teranishi, A. Y.; Williams, D. R. *J. Am. Chem. Soc.* **1971**, *93*, 3303. (b) Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, 520; (c) *J. Org. Chem.* **1979**, *44*, 1574.

(4) Gossauer, A. "Die Chemie der Pyrrole"; Springer-Verlag: Berlin, 1974. Jones, R. A.; Bean, G. P. "The Chemistry of Pyrroles"; Academic Press: London, 1977.

(5) Murahashi, S.; Shimamura, T.; Moritani, I. *J. Chem. Soc., Chem. Commun.* **1974**, 931.

(6) Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821. Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230. Trost, B. M.; Genet, J. P. *J. Am. Chem. Soc.* **1976**, *98*, 8516. Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451. For amination of preformed π-allyl complexes see: Akermark, B.; Zetterberg, K. *Tetrahedron Lett.* **1975**, 3733; Akermark, B.; Backvall, J. E.; Lowenborg, A.; Zetterberg, K. *J. Organomet. Chem.* **1979**, *166*, C33.

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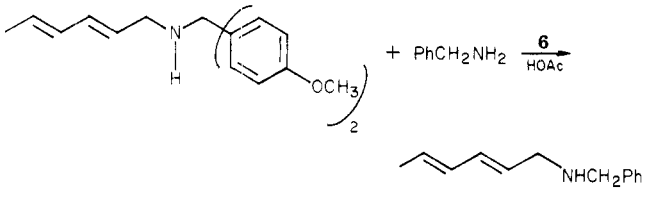
2. Reaction of 2 with benzylamine at room temperature in the presence of tetrakis(triphenylphosphine)palladium (6) produced a mixture of two compounds, the simple alkylation product 4 and the desired pyrrole 5. Increased reaction times did not increase the amount of pyrrole at the expense of 4, suggesting that the latter is not the precursor of the pyrrole. In fact, the conversion of 4 to pyrrole, which requires an isomerization around the double bond, proved surprisingly difficult. Since we did expect that the initial alkylation of 2 would produce an isomeric mixture of 3 and 4, it is likely that 3 cyclized as it formed to give the pyrrole directly.[7]

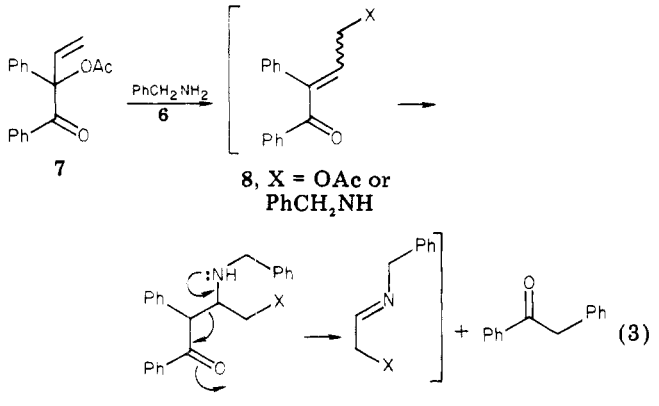
Attempts to induce 4 to isomerize to 3 and consequently cyclize to 5 with base failed. Partial success was achieved by use of a mixture of DABCO and thiophenol in which a 1:1 mixture of pyrrole 5 and the Michael addition product was obtained. The entire problem was circumvented when we found that the pyrrole was the only product when the initial alkylation was performed at reflux instead of room temperature. Substitution of the somewhat higher boiling solvent toluene for THF does lead to some improvement in yield from 53 to 60%. As summarized in Table I, this method produces comparable results when applied to the requisite allylic acetate from benzil or cyclohexane-1,2-dione.

The isomerization of 4 to 3 by the palladium(0) catalysts is somewhat surprising. A possible explanation invokes reformation of the intermediate π-allyl complex from protonated 4 at the higher temperature. To test the idea that allyl ammonium salts are substrates for 6, we treated 4,4′-dimethoxybenzhydrylsorbylamine with benzylamine



and 6 in refluxing THF. No reaction took place until a stoichiometric amount of acetic acid was added, at which point amine exchange occurred to give benzylsorbylamine. This result suggests that we can extend the palladium-based allylic alkylations to allylic amines.[8]

In the reaction of the substrate from benzil, i.e., 7, deoxybenzoin was isolated in addition to 1-benzyl-2,3-diphenylpyrrole. Equation 3 provides a rationale for this

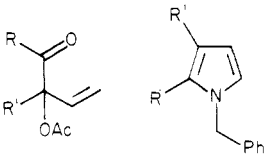


(7) Scheimer, P.; Chapman, O. L.; Lassila, J. D. *J. Org. Chem.* **1969**, *34*, 813.

(8) For reviews see: Trost, B. M. *Tetrahedron* **1977**, *33*, 2615; *Pure Appl. Chem.* **1979**, *51*, 787.

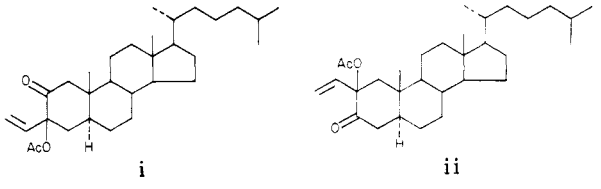
(9) (a) Remers, W. A.; Roth, R. H.; Gibs, G. J.; Weiss, M. J. *J. Org. Chem.* **1971**, *36*, 1232. (b) Kondo, K.; Matsumoto, M. *Chem. Lett.* **1974**, 701.

Table I. Synthesis of *N*-Benzylpyrroles from Allyl Acetates



entry	R	R′	solvent[a]	% yield
1	CH_3	CH_3	THF	53
			$PhCH_3$	60
2	Ph	Ph	THF	43[b,f]
			$PhCH_3$	47[b,f]
3		$(CH_2)_4$	THF	58[e]
4	Ph	H	THF	65
5	H	Ph	THF	9
6[g]			THF	33[c]
7[g]			PhH	28[d]

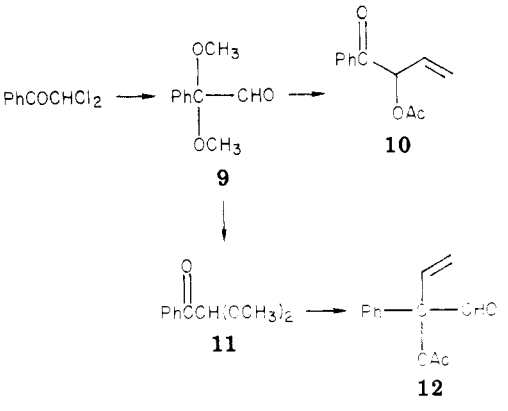
[a] All reactions were performed at the reflux temperature of the indicated solvent except for entry 4. [b] Deoxybenzoin was also isolated in 27%. [c] Product is 20. [d] Product is 16. [e] Reference 9a. [f] Reference 9b. [g] Starting materials for entries 6 and 7 are i and ii, respectively.



i ii

rather remarkable degradation reaction. The observance of such a reaction only in the case of 7 may stem from the fact that the enone system created in the intermediate 8 (X = OAc or $PhCH_2NH$) should be an exceptionally good Michael acceptor.

Extension of the method to unsymmetrical α-diketones requires the generation of differentially protected systems. For example, the ketal 9 of phenylglyoxal is available from



dichloroacetophenone[10] upon treatment with methanolic sodium methoxide.[11] Addition of vinylmagnesium bromide to 9 and acetylation of the resultant alcohol in the presence of DMAP proceeded smoothly. Deketalization to form 10 without decomposition required the use of a few drops of aqueous perchloric acid in acetone. Subjection of 10 to benzylamine in the presence of a catalytic amount of 6 led exclusively to 1-benzyl-2-phenylpyrrole. Alternatively, 1-benzyl-3-phenylpyrrole was available from 12, which, in turn, arose by Grignard addition to acetal 11,

(10) Aston, J. G.; Newkirk, J. D.; Jenkins, D. M.; Dorsky, J. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, p 538.

(11) Henery-Logan, K. R.; Fridinger, T. L. *Chem. Commun.* **1968**, 130. Roulet, C.; Levas, E. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *269*, 996.

Scheme I. Preparation of Functiodifferentiated α-Diketones and Pyrrole Annulation

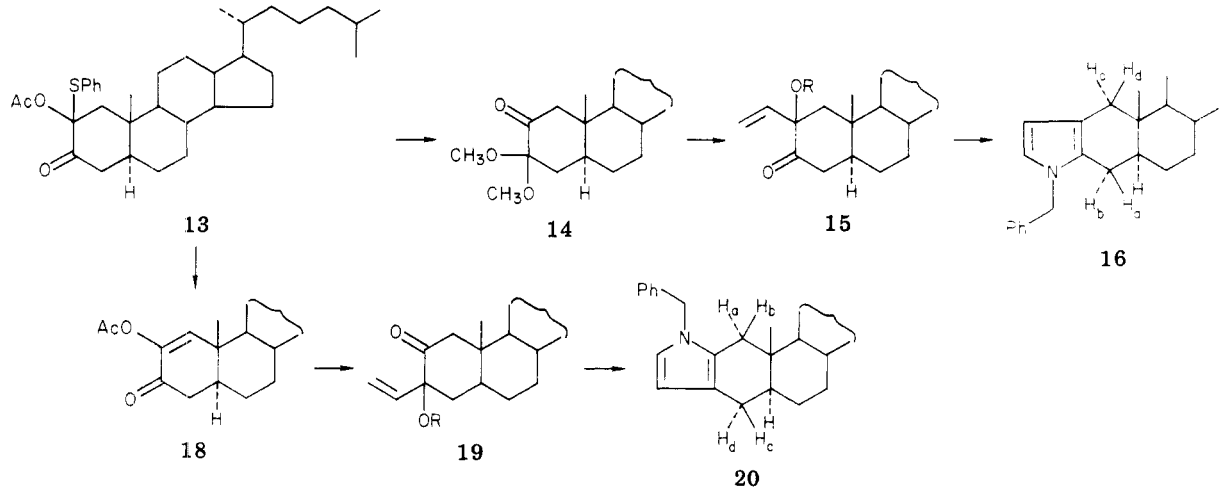
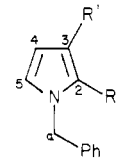


Table II. ^{13}C NMR Data of Pyrroles[a]

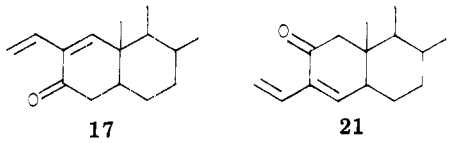


compd	C(2)	C(3)	C(4)	C(5)	a
R,R′ = $(CH_2)_4$	123.5	113.6	102.8	115.3	48.2
R = Ph, R′ = H	137.8	109.0	109.4	123.3	51.1
R = H, R′ = Ph	117.9	125.2	106.6	122.2	53.6
R = R′ = Ph	136.6	122.9	107.8	121.5	50.6
16	126.5	116.8	106.9	119.4	49.8
20	127.7	116.2	105.9	119.6	49.9

[a] All chemical shifts are in parts per million relative to internal Me_4Si.

hydrolysis with *p*-toluenesulfonic acid in acetone, and then acetylation. Acetal **11** is readily available by direct acetalization of phenylglyoxal. The substitution pattern of the pyrroles is clearly established by both ^1H (see Experimental Section) and ^{13}C (see Table II) NMR data.[12]

We recently reported a functiodifferentiated α-diketone synthesis from β-keto sulfides.[1a,13] Sulfenylation and acetoxylation of 5α-cholestanone gave **13** (see Scheme I). Treatment of **13** with iodine in methanol gave the monoketal **14** exclusively. Obtention of **14** allowed selective addition of vinylmagnesium bromide to C(2). Hydrolysis of the ketal to give **15a** must precede acetylation to give **15b**, the requisite substrate for pyrrole **16**. The major byproduct in the palladium reaction appeared to be dienone **17** which was tentatively assigned on the basis of



17 21

the proton NMR spectrum which showed a vinyl region consistent with this assignment [δ 7.18 (s, 1 H), 6.56 (dd, J = 18, 11 Hz, 1 H), 5.70 (dd, J = 18, 2 Hz, 1 H), 5.18 (dd, J = 11, 2 Hz, 1 H)].

The alternative regioisomer took advantage of the fact that **13** represents a functiodifferentiated α-diketone of the reverse order. Attempts to add vinylmagnesium bromide directly to **13** led to complex reaction mixtures, presumably because the C(2) ketone was unmasked during the process. The mono enol acetate **18** would also suffer attack of the Grignard reagent, but this time the carbonyl group is generated in a protected form, its corresponding enolate, which would be inert to attack of the Grignard reagent. Oxidation of **13** with MCPBA at −78 °C, allowing the reaction to warm and then reflux, led directly to the single diosphenol acetate **18** in 78% yield. Addition of excess vinyllithium folowed by acetylation gave the desired substrate **19b** in 63% yield. Here too, the palladium-catalyzed pyrrole formation was accompanied by a byproduct, tentatively identified as **21** on the basis of analogy and its proton NMR spectrum. However **21** was not obtained pure and thus was not examined further.

The regiochemistry of **16** and **20** stemmed from the method of synthesis. The proton NMR spectra at 270 MHz also allowed differentiation. In each case, three of the four protons at C(1) and C(4) of the steroid are clearly visible [**16**: δ 2.32 (dd, J = 15.8, 5.4 Hz, H_b), 2.18 (d, J = 15 Hz, H_c), 2.53 (d, J = 15 Hz, H_d). **20**: δ 2.38 (d, J = 15 Hz, H_b), 2.17 (dd, J = 15, 12 Hz, H_c), 2.43 (dd, J = 15, 5 Hz, H_d)]. The axial proton proximal to the *N*-benzyl group (H_a in **16** and **20**) is not clearly discernible but is tentatively assigned at δ 1.98 (br t, $J \simeq 15$ Hz) and 2.02 (d, $J \simeq 15$ Hz), respectively. Thus, in **16** H_b appears as a doublet of doublets with coupling to both H_a and C_5H, indicating that the nitrogen is at C(3), and in **20** H_b appears only as a doublet with coupling only to H_a, indicating that the nitrogen is at C(2).

With the ability to create selectively protected α-dicarbonyl compounds from simple ketones, this approach represents an annulation of a pyrrole onto any aldehyde or ketone bearing an α-methylene group.[17] By utilization of substituted vinyl Grignard reagents, variation of virtually any substituent, R^1–R^4 (eq 4), should be feasible. The

(12) Page, T. F., Jr.; Alger, T.; Grant, D. M. *J. Am. Chem. Soc.* **1965**, *87*, 5333. Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1968**, *90*, 3543. Lippmia, E.; Magi, M.; Novikov, S. S.; Khmelnitski, L. I.; Prihodko, A. S.; Lebedev, O. V.; Epishina, L. V. *Org. Magn. Reson.* **1972**, *4*, 153, 192. Martin, L. L.; Chang, C.-J.; Floss, H. G.; Mabe, J. A.; Hagaman, E. W.; Wenkert, E. *J. Am. Chem. Soc.* **1972**, *94*, 8942.

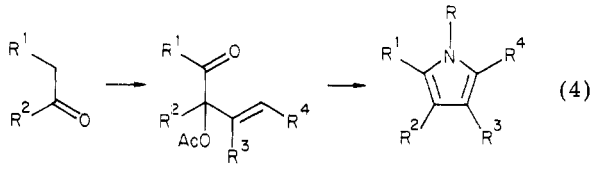
(13) Trost, B. M.; Bridges, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 5017.

(14) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

(15) Griffiths, D. W.; Gutsche, C. D. *J. Org. Chem.* **1971**, *36*, 2184.

(16) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1966**, *31*, 351.

(17) Cf. Michaleva, A. I.; Trofimov, B. A.; Vaselev, A. N. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1979**, 197. Wang, C. B.; Chang, C. K. *Synthesis* **1979**, 548.



(4)

known compatibility of the palladium-based methodology with many functional groups suggests that this will be a chemoselective approach to pyrroles.[18] Extension to olefins and acetylenes also follows since conversion of such functional groups to α-diketones is known.[3]

Experimental Section

General. All reactions were run under a positive nitrogen pressure. THF was distilled from sodium benzophenone ketyl. Silica gel, Macherey Nagel MN-Kieselgel P/UV$_{254}$, was employed for all analytical and preparative TLC. IR spectra were taken on a PE 267 spectrometer. NMR spectra were taken on a JEOLCO MH-100, Brucker 270 MHz, or JEOLCO FX-60/^{13}C spectrometer. Mass spectra were obtained on a MS 902. Melting points are uncorrected. Tetrakis(triphenylphosphine)palladium was prepared by the method of Coulson.[14] α,α-Dichloroacetophenone was prepared by the method of Aston et al.[10] 2-Acetoxy-2-(phenylthio)-5α-cholestan-3-one and 3,3-dimethoxy-5α-cholestan-2-one were prepared by the method of Trost and Massiot.[1a]

Addition of Vinylmagnesium Bromide to 1,2-Diketones and Acetylation. Addition to Biacetyl. A solution of 21.4 mmol of vinylmagnesium bromide in 20 mL of THF was added to 1.53 g (17.8 mmol) of biacetyl in 20 mL of THF at room temperature. After 3 h, the reaction was quenched with aqueous ammonium chloride and extracted with chloroform. The chloroform extract was filtered through a short column of silica gel and the silica gel eluted with additional chloroform. After evaporation, the resulting crude oil was dissolved in 30 mL of dry pyridine to which was added 10 mL of acetic anhydride and 50 mg of DMAP. After the resultant solution was stirred for 26 h at room temperature, it was poured into an ether–ice water mixture. The water was washed with additional ether and the ether phase filtered through a short silica gel column to give, after Kugelrohr distillation at 60–80 °C (pot temperature) (15 mm), 1.25 g (45%) of acetate **2** as a colorless oil, pure by NMR and VPC (15% Carbowax 20M on Chromosorb W at 165 °C): NMR ($CDCl_3$) δ 1.55 (s, 3 H), 2.06 (s, 3 H), 2.11 (s, 3 H), 5.26 (d, J = 11 Hz, 1 H), 5.38 (d, J = 17 Hz, 1 H), 5.99 (dd, J = 17, 11 Hz, 1 H); IR (neat) 1740, 1715, 1640, 990, 945, 865, 715 cm^{-1}; mass spectrum, m/e (relative %) 149 (3), 111 (3), 97 (7), 95 (9), 83 (12), 81 (11), 71 (14), 69 (19), 67 (10), 60 (12), 57 (46), 55 (47), 45 (23), 44 (32), 43 (100).

Addition to Benzil. A solution of 19.2 g (91.4 mmol) of benzil in 50 mL of THF was added to 100.6 mmol of vinylmagnesium bromide in 50 mL of THF at room temperature. After being refluxed for 2 h, the reaction was quenched with saturated aqueous ammonium chloride and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated in vacuo and the residue distilled on a Kugelrohr apparatus (bath temperature 140 °C (0.4 mm)) to give 15.54 g of a 4:7 mixture (by integration of the vinyl protons) of the alcohol (78% based upon recovered starting material) and benzil (52% recovery). For characterization and small-scale experiments, samples of pure alcohol were obtained by preparative TLC using 50:1 chloroform–ethyl acetate: NMR ($CDCl_3$) δ 5.06 (s, 1 H), 5.39 (dd, J = 10.5, 1.5 Hz, 1 H), 5.76 (dd, J = 17.5, 1.5 Hz, 1 H), 6.60 (dd, J = 17.5, 10.5 Hz, 1 H), 7.34 (m, 8 H), 7.74 (m, 2 H); IR (neat) 3450, 1740, 1665, 1597, 1580, 1495 cm^{-1}; exact mass calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0991. Note that marked changes in the chemical shifts as a function of the dryness of the sample were observed. Before the sample was vacuum dried, the NMR spectrum was the following: δ 4.02 (dd, J = 8, 2 Hz, 1 H) 4.25 (dd, J = 14, 2 Hz, 1 H), 5.96 (s, 1 H), 6.42 (dd, J = 14, 8 Hz, 1 H).

A solution of 643 mg (2.70 mmol) of 3-hydroxy-3,4-diphenylbut-1-en-4-one in 30 mL of pyridine containing 10 mL of acetic anhydride and 200 mg of DMAP was stirred for 36 h at room temperature. After the usual workup and Kugelrohr distillation (bath temperature 90–110 °C (0.25 mm)), 797 mg of **7** was obtained as an oil which crystallized upon standing. Recrystallization from ether–hexane gave 624 mg (82%) of **7**, mp 89–91 °C. On large scales in which the mixture of alcohol and benzil were acetylated, separation was achieved by first crystallization of benzil from ethanol and then crystallization of the mother liquors from ether–hexane: NMR ($CDCl_3$) δ 1.97 (s, 3 H), 4.88 (d, J = 18 Hz, 1 H), 5.24 (d, J = 11 Hz, 1 H), 6.92 (dd, J = 18, 11 Hz, 1 H), 7.24 (m, 6 H), 7.42 (m, 2 H), 7.67 (m, 2 H); IR (KBr) 1735, 1687, 1635, 1595, 1580, 980, 930, 895 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75; mol wt, 280.1099. Found: C, 77.21; H, 5.71; mol wt, 280.1071.

Addition to Cyclohexane-1,2-dione. As in the case of biacetyl, 5.04 g (45 mmol) of the cyclohexane-1,2-dione was reacted with 54 mmol of vinylmagnesium bromide in 60 mL of THF and the resultant crude alcohol directly acetylated in 100 mL of pyridine containing 40 mL of acetic anhydride and 1.7 g of DMAP to give, after Kugelrohr distillation (bath temperative 80–100 °C (0.5 mm)) and preparative TLC (1:2 ethyl acetate–hexane), 3.35 g (41%) of 2-acetoxy-2-vinylcyclohexanone: NMR ($CDCl_3$) δ 1.5–2.5 (m, 8 H), 2.08 (s, 3 H), 5.20 (br d, J = 11.5, 1 H), 5.22 (br d, J = 18.3 Hz, 1 H), 6.28 (dd, J = 18.3, 11.5 Hz, 1 H); IR (neat) 1740, 1725, 1630, 970, 845, 810, 780 cm^{-1}; exact mass calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0932.

Preparation of 1-Phenyl-2-acetoxy-3-buten-1-one. α,α-Dichloroacetophenone (59 g, 0.31 mol) was added to 33.9 g (0.628 mol) of sodium methoxide in 400 mL of methanol at 0 °C. After the mixture was stirred at room temperature overnight, the solvent was removed in vacuo and the residue taken up in ether. Washing the ether layer with brine, drying (Na_2SO_4), and distilling at 120–125 °C (6 mm) gave a mixture of 2,2-dimethoxyphenylacetaldehyde and starting dichloride which was carefully fractionated at 115–118 °C (6 mm) to give 26 g of ketal aldehyde and at 120–125 °C (6 mm) to give 13 g of recovered starting materials. Ketal: NMR δ 3.26 (s, 6 H), 7.4 (m, 5 H), 9.28 (s, 1 H).

The aldehyde (9.0 g, 0.050 mol) was reacted with 0.25 mol of vinylmagnesium bromide as above to give, after filtering through silica gel with chloroform and distillation via a Kugelrohr apparatus (bath temperature 70–90 °C (0.6 mm)), 9.2 g (88%) of 1,1-dimethoxy-1-phenyl-2-hydroxy-3-butene: NMR ($CDCl_3$) δ 2.46 (br s, 1 H), 3.17 (s, 3 H), 3.34 (s, 3 H), 4.46 (br d, J = 5 Hz, 1 H), 5.06 (dm, J = 10 Hz, 1 H), 5.12 (dm, J = 16 Hz, 1 H), 5.70 (m, 1 H), 7.3 (m, 5 H).

The crude alcohol (2.25 g, 10.8 mmol) was acetylated in the usual fashion with 15 mL of acetic anhydride and 100 mg of DMAP in 25 mL of dry pyridine to give 2.68 g (quantitative yield) of crude acetate which was purified by Kugelrohr distillation (bath temperature 110–115 °C (0.5 mm)) to give 1.33 g (49%) of 1,1-dimethoxy-1-phenyl-2-acetoxy-3-butene.

A solution of 490 mg (1.96 mmol) of the above ketal acetate in 2 mL of acetone-d_6 was placed in a NMR tube. Upon addition of 1 drop of 60% aqueous perchloric acid and obtention of the NMR spectrum, the reaction appeared to be complete. The solution was poured into ether–aqueous sodium bicarbonate and the ether layer passed through a silica gel column, eluting with ether. After evaporation of the ether, the residue was further purified by Kugelrohr distillation (bath temperature 80–100 °C (0.3 mm)) to give 379 mg (95%) of the title compound: NMR ($CDCl_3$) δ 2.10 (s, 3 H), 5.38 (br d, J = 10 Hz, 1 H), 5.51 (br d, J = 17 Hz, 1 H), 6.01 (ddd, J = 17, 10, 6 Hz, 1 H), 6.34 (br d, J = 6 Hz, 1 H), 7.47 (m, 3 H), 7.96 (m, 2 H). The instability of the compound required its direct use in the palladium reaction.

Preparation of 2-Acetoxy-2-phenyl-3-butenal (12). 2,2-Dimethoxyphenylacetaldehyde (5.59 g) dissolved in 40 mL of acetone containing 13 drops of concentrated hydrochloric acid was hydrolyzed quantitatively to phenylglyoxal (Kugelrohr distilled, bath temperature 60–80 °C (0.8 mm)). It was directly acetalized as described[15] to give 5.02 g (90%) of α,α-dimethoxyacetophenone. Vinylmagnesium bromide (205 mmol) was added to 4.77 g (26.5 mmol) of the acetal in the usual fashion to give

(18) For a few additional recent pyrrole syntheses, see: Berner, H.; Schulz, G.; Reinshagen, H. *Monatsch. Chem.* **1977**, *108*, 233, 285; Engel, N.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 676; Oleson, S. O.; Madsen, J. O.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 535.

(19) Allen, C. F. H.; Barker, W. E. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 156.

4.57 g (83%) of 1,1-dimethoxy-2-hydroxy-2-phenyl-3-butene after Kugelrohr distillation (bath temperature 70–90 °C (0.3 mm)): NMR ($CDCl_3$) δ 2.88 (s, 1 H), 3.28 (s, 3 H), 3.38 (s, 3 H), 4.28 (s, 1 H), 5.26 (dd, J = 10.5, 1.5 Hz, 1 H), 5.42 (dd, J = 17.5, 1.5 Hz, 1 H), 6.44 (dd, J = 17.5, 10.5 Hz, 1 H), 7.30 (m, 3 H), 7.53 (m, 2 H). The hydroxy acetal (315 mg, 1.51 mmol) in 10 mL of acetone and 2 mL of water containing 150 mg of $TsOH \cdot H_2O$ was refluxed for 11 h. Solid sodium bicarbonate was added, and the reaction was filtered and then evaporated in vacuo. The residue, dissolved in chloroform, was filtered through a short silica gel column to give, after Kugelrohr distillation (bath temperature 60–70 °C (0.4 mm)), 211 mg (86%) of aldehyde. Attempted purification of this aldehyde by TLC led to substantial decomposition: NMR ($CDCl_3$) δ 4.10 (s, 1 H), 5.41 (dd, J = 11, 1 Hz, 1 H), 5.53 (dd, J = 17.5, 1 Hz, 1 H), 6.26 (dd, J = 17.5, 11 Hz, 1 H), 7.4 (m, 5 H), 9.58 (s, 1 H); IR (neat) 3480, 2840, 1725, 1640, 1600, 1490 cm^{-1}.

The hydroxy aldehyde (95 mg, 0.59 mmol) was acetylated with 0.30 mL of acetic anhydride and 80 mg of DMAP in 5 mL of methylene chloride and 1 mL of pyridine to give, after the usual workup and Kugelrohr distillation (bath temperature 85–95 °C (0.6 mm)), 98 mg (82%) of **12**: NMR ($CDCl_3$) δ 2.22 (s, 3 H), 5.37 (dd, J = 17.5, 1 Hz, 1 H), 5.46 (dd, J = 11, 1 Hz, 1 H), 6.55 (dd, J = 17.5, 11 Hz, 1 H), 7.4 (m, 5 H), 9.50 (s, 1 H); IR (neat) 2840, 2720, 1735, 1725, 1645, 1600, 1495 cm^{-1}; exact mass calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0786.

Preparation of 2-Acetoxy-2-vinyl-5α-cholestan-3-one (15b). A solution of ~10 mmol of vinylmagnesium bromide in 20 mL of dry THF was added to 632 mg (1.4 mmol) of 3,3-dimethoxy-5α-cholestan-2-one (**14**).[1a] After the usual workup, there was obtained 687 mg of oil after passage of the residue through a short silica gel column. This oil (600 mg) was dissolved in 10 mL of acetone containing 4 drops of concentrated HCl. After the mixture was stirred for 1 h at room temperature, evaporation in vacuo gave 600 mg of crude **15a** which showed only one isomer by TLC and proton NMR [δ 5.12 (d, J = 10 Hz, 1 H), 5.32 (d, J = 17 Hz, 1 H), 5.96 (dd, J = 17, 10 Hz, 1 H)]. Acetylation of 557 mg of **15a** in 30 mL of pyridine with 15 mL of acetic anhydride and 50 mg of DMAP gave, after the usual workup and purification by preparative TLC (1:1 ether–hexane), 412 mg (76% overall from **14**) of **15b**: NMR (270 MHz, $CDCl_3$, partial) 0.66 (s, 3 H), 0.86 (d, J = 6.6, 6 H), 0.89 (d, J = 6.5 Hz, 3 H), 1.16 (s, 3 H), 2.12 (s, 3 H), 5.16 (d, J = 18 Hz, 1 H), 5.21 (d, J = 11 Hz, 1 H), 6.38 (dd, J = 18, 11 Hz, 1 H); exact mass calcd for $C_{31}H_{50}O_3$ 470.3760, found 470.3759.

Preparation of 3-Acetoxy-3-vinyl-5α-cholestan-2-one. A solution of 88 mg (0.43 mmol) of MCPBA in the 2 mL of methylene chloride was added to a −78 °C solution of 229 mg (0.41 mmol) of 2-acetoxy-2-(phenylthio)-5α-cholestan-3-one (**13**) in 4 mL of methylene chloride. After 30 min at −78 °C, 30 min at room temperature, and 11 h at reflux, the mixture was poured into an ether–aqueous sodium bicarbonate mixture. The ether layer was washed with brine, dried (Na_2SO_4), and evaporated in vacuo. Filtration of the residue through a short silica gel column and recrystallization (C_2H_5OH) gave 223 mg (78%) of **18** as needles, mp 137–138 °C. While no melting point is given in the literature, the IR and NMR spectral data agree.[16]

To a −94 °C (hexane, liquid N_2) solution of vinyllithium (prepared from 760 mg, 7.1 mmol, of vinyl bromide and 3.18 mmol of *tert*-butyllithium in pentane) in 10 mL of ether was added dropwise 123 mg (0.28 mmol) of **18** dissolved in 5 mL of ether. Upon completion of the addition, the reaction was allowed to warm to 0 °C (~2 h) and poured via a cannula into saturated aqueous ammonium chloride. It was taken up in chloroform and the latter solution washed with water and filtered through a short silica gel column, eluting with additional chloroform. After evaporation of chloroform, 151 mg of **19a**, a colorless oil, homogeneous by TLC, was obtained and taken directly onto the next step: NMR (partial, $CDCl_3$) δ 2.24 (d, J = 13 Hz, 1 H), 2.51 (d, J = 13 Hz, 1 H), 5.23 (d, J = 11 Hz, 1 H), 5.40 (d, J = 17 Hz, 1 H), 6.15 (dd, J = 17, 11 Hz, 1 H). The alcohol **19a** was acetylated in the usual fashion with 0.3 mL of acetic anhydride and 120 mg of DMAP in 7 mL of methylene chloride and 1 mL of pyridine to give 82 mg (63% from **18**) of **19b** as a colorless gum: NMR (partial, $CDCl_3$) δ 2.09 (s, 3 H), 5.34 (d, J = 10.5 Hz, 1 H), 5.40 (d, J = 17 Hz, 1 H), 6.08 (dd, J = 17, 10.5 Hz, 1 H); IR ($CHCl_3$) 1740, 1715, 1640 cm^{-1}; exact mass calcd for $C_{31}H_{50}O_3$ 470.3760, found 470.3759.

Preparation of Pyrroles. 1-Benzyl-2,3-dimethylpyrrole. A solution of 257 mg (1.65 mmol) of **2**, 300 mg (2.80 mmol) of benzylamine, and 226 mg (0.19 mmol) of tetrakis(triphenylphosphine)palladium in 5 mL of dry THF was stirred for 3 h at room temperature and 20 h at reflux. Silica gel was added and the slurry added to a 15 × 2.5 cm column of silica gel and eluted rapidly with hexane (some decomposition on the column was noted by the column becoming red) to give after evaporation 162 mg (53%) of colorless needles, mp 37–38 °C. Sublimation at 60–80 °C (0.2 mm) did not change the melting point: NMR ($CDCl_3$) δ 2.04 (s, 6 H), 4.98 (s, 2 H), 6.01 (d, J = 2.8 Hz, 1 H), 6.58 (d, J = 2.8 Hz, 1 H), 7.0 (m, 2 H), 7.28 (m, 3 H); NMR (C_6D_6) δ 1.82 (s, 3 H), 2.12 (s, 3 H), 4.48 (s, 2 H), 6.18 (d, J = 2.8 Hz, 1 H), 6.45 (d, J = 2.8 Hz, 1 H), 6.77 (m, 2 H), 6.94 (m, 3 H); IR 1610, 1575, 1495 cm^{-1}; UV (C_2H_5OH) λ_{max} 205 nm (ε 17 400), 258 (820), 263 (710), 269 (470); exact mass calcd for $C_{13}H_{15}N$ 185.1204, found 185.1201.

Repetition of the experiment with 259 mg (1.66 mmol) of **2**, 206 mg (1.92 mmol) of benzylamine, and 172 mg (0.15 mmol) of catalyst in 5 mL of toluene at reflux for 1 h and workup on Florisil, eluting with 4:1 hexane–ether, gave 183 mg (60%) of crystalline pyrrole.

1-Benzyl-2,3-Diphenylpyrrole. As above, 236 mg (0.84 mmol) of **7**, 196 mg (1.83 mmol) of benzylamine, and 196 mg (0.17 mmol) of catalyst were refluxed in 5 mL of THF to give 106 mg of crystalline pyrrole after elution through Florisil with hexane and 231 mg of a mixture of pyrrole and deoxybenzoin after elution of the column with ethyl acetate. The latter was separated by preparative TLC (50:1 chloroform–ethyl acetate) to give 5 mg of pyrrole (total 111 mg, 43%) and 44 mg (27%) of deoxybenzoin, identical by NMR, IR, and melting point [mp 53.5–54.5 °C (lit.[19] mp 55–56 °C)] with an authentic sample. The pyrrole was recrystallized from hexane: mp 117–118 °C; NMR ($CDCl_3$) δ 4.88 (s, 2 H), 6.43 (d, J = 3 Hz, 1 H), 6.68 (d, J = 3 Hz, 1 H), 6.8–7.3 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 50.6, 107.8, 121.5, 122.9, 125.0, 126.0, 126.7, 127.2, 127.6, 127.9, 128.4, 130.8, 131.2, 133.2, 136.6, 138.5, 139.1; IR (KBr) 1600, 1495, 1455 cm^{-1}; UV (C_2H_5OH) λ_{max} 205 nm (ε 42 000), 246 (15 300), 285 (9500); exact mass calcd for $C_{23}H_{19}N$ 309.1517, found 309.1509.

1-Benzyl-4,5,6,7-tetrahydroindole. As above, 525 mg (2.88 mmol) of 2-acetoxy-2-vinylcyclohexanone was reacted with 412 mg (3.85 mmol) of benzylamine and 166 mg (0.14 mmol) of palladium catalyst in 5 mL of THF at room temperature for 1 h and at reflux for 5 h to give, after chromatography on Florisil eluting with chloroform and Kugelrohr distillation (bath temperature 110–120 °C (0.6 mm)), 352 mg (58%) of the above pyrrole as a colorless oil: NMR ($CDCl_3$) δ 1.72 (m, 4 H), 2.45 (m, 2 H), 4.88 (s, 2 H), 5.90 (d, J = 3 Hz, 1 H), 6.48 (d, J = 3 Hz, 1 H), 6.96 (m, 2 H), 7.20 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 21.0, 22.5, 22.6, 22.8, 48.2, 102.8, 113.6, 115.3, 122.2, 122.8, 123.5, 124.2, 133.8; IR (neat) 1605, 1495, 1485 cm^{-1}; UV (C_2H_5OH) λ_{max} 207 nm (ε 15 500), 258 (1130), 264 (920), 270 (700), 310 (620); exact mass calcd for $C_{15}H_{17}N$ 211.1361, found 211.1352.

Pyrrole 16. As above, 147 mg (0.31 mmol) of keto acetate **15b** was reacted with 67.4 mg (0.63 mmol) of benzylamine and 114 mg (0.098 mmol) of palladium catalyst in 3 mL of benzene to give, after filtering through a Florisil column eluting with chloroform and preparative TLC (1:2 ether–hexane), 33 mg (26%) of a fraction tentatively identified as dienone **17** and 43 mg (28%) of crystalline pyrrole **16**: mp 135–136 °C (ether-ethanol); NMR ($CDCl_3$, 270 MHz, partial) 0.67 (s, 3 H), 0.72 (s, 3 H), 0.85 (d, J = 6.4 Hz, 3 H), 0.86 (d, J = 6.4 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 2.18 (d, J = 15 Hz, 1 H), 2.32 (dd, J = 15.8, 5.4 Hz, 1 H), 2.53 (d, J = 15 Hz, 1 H), 4.94 (s, 2 H), 5.94 (d, J = 2.6 Hz, 1 H), 6.53 (d, J = 2.6 Hz, 1 H), 6.95 (br d, J = 7 Hz, 2 H), 7.26 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 12.0, 18.7, 21.3, 22.5, 22.7, 23.9, 24.3, 26.6, 28.0, 29.5, 31.9, 35.8, 36.2, 37.9, 39.5, 40.1, 42.5, 49.8, 54.0, 56.4, 106.9, 116.9, 119.4, 126.3, 126.5, 127.0, 128.5, 138.8; IR (KBr) 1490, 1467, 1457 cm^{-1}; exact mass calcd for $C_{36}H_{53}N$ 499.4178, found 499.4177.

Pyrrole 20. As above, 69 mg (0.25 mmol) of keto acetate **19b**, 54.6 mg (0.51 mmol) of benzylamine, and 112 mg (0.094 mmol) of palladium catalyst in 3 mL of THF gave, after preparative TLC (1:2 ether–hexane), 22 mg (21%) of an impure sample tentatively identified as dienone **21** and 24 mg (33%) of pyrrole **20**: NMR ($CDCl_3$, 270 MHz, partial) δ 0.65 (s, 3 H), 0.73 (s, 3 H), 0.85 (d, J = 6.4 Hz, 3 H), 0.86 (d, J = 6.4 Hz, 3 H), 0.89 (d, J = 7.7 Hz,

3 H), 2.17 (dd, J = 15, 12 Hz, 1 H), 2.38 (d, J = 15 Hz, 1 H), 2.43 (dd, J = 15, 5 Hz, 1 H), 4.93 (s, 2 H), 5.93 (d, J = 2.6 Hz, 1 H), 6.53 (d, J = 2.6 Hz, 1 H), 6.95 (br d, J = 7 Hz, 2 H), 7.26 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 12.0, 18.7, 21.2, 22.5, 22.8, 23.9, 24.3, 28.0, 28.3, 29.3, 29.7, 31.9, 35.8, 36.2, 36.6, 39.6, 40.1, 42.5, 42.8, 49.9, 54.0, 56.4, 105.9, 116.2, 119.6, 126.4, 127.1, 127.7, 128.5, 138.8; IR ($CHCl_3$) 1445, 1380, 1370, 1355, 1320 cm^{-1}; exact mass calcd for $C_{36}H_{53}N$ 499.4178, found 499.4182.

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Registry No. **2**, 73770-26-0; **5**, 73770-27-1; **7**, 73770-28-2; **12**, 73770-29-3; **13**, 63608-54-8; **14**, 27335-83-7; **15a**, 73770-30-6; **15b**, 73770-31-7; **16**, 73789-31-8; **17**, 73770-32-8; **18**, 5011-78-9; **19a**, 73770-33-9; **19b**, 73770-34-0; **20**, 73770-35-1; **21**, 73789-32-9; vinyl bromide, 593-60-2; biacetyl, 431-03-8; benzil, 134-81-6; 3-hydroxy-3,4-diphenylbut-1-en-4-one, 30935-15-0; cyclohexane-1,2-dione, 765-87-7; 2-acetoxy-2-vinylcyclohexanone, 73770-36-2; 1-phenyl-2-acetoxy-3-buten-1-one, 73770-37-3; α,α-dichloroacetophenone, 2648-61-5; 2,2-dimethoxyphenylacetaldehyde, 19159-39-8; 1,1-dimethoxy-1-phenyl-2-hydroxy-3-butene, 73770-38-4; 1,1-dimethoxy-1-phenyl-2-acetoxy-3-butene, 73770-39-5; α,α-dimethoxyacetophenone, 6956-56-5; 1,1-dimethoxy-2-hydroxy-2-phenyl-3-butene, 73770-40-8; 2-hydroxy-3-phenyl-3-butenal, 73770-41-9; benzylamine, 100-46-9; tetrakis(triphenylphosphine)palladium, 14221-01-3; 1-benzyl-2,3-diphenylpyrrole, 53646-89-2; deoxybenzoin, 614-29-9; 1-benzyl-4,5,6,7-tetrahydroindole, 27866-39-3.

Syntheses of Dihydropyrenes with Functionality in the Cavity of the π-Electron Cloud

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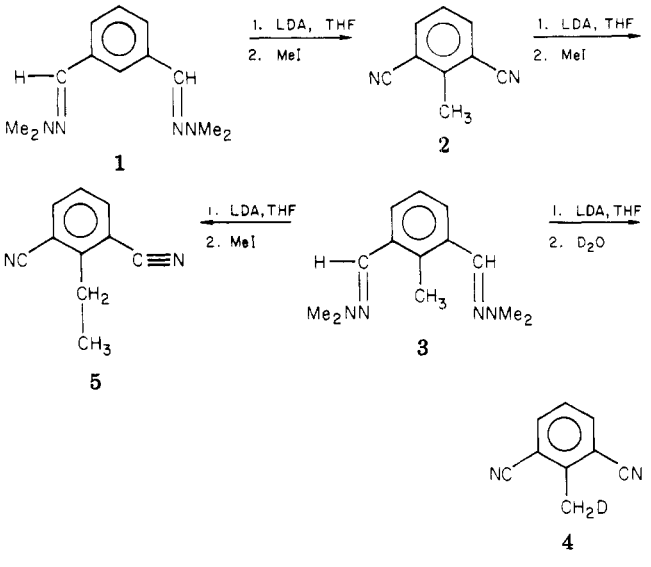
The cyano group is shown to be a good group for directing ortho lithiation and, with 2,6-dicyanotoluene as starting material, ortho lithiation provides easy access to a variety of 1,2,3-trisubstituted benzene derivatives. The use of such derivatives in the standard thiacyclophane synthesis of dihydropyrenes has provided in good yield *trans*-15-(4'-butenyl)-16-methyldihydropyrene (**14a**) and *trans*-15-(methoxyethyl)-16-methyldihydropyrene (**14b**), the first examples of dihydropyrenes having functionality within the cavity of the aromatic π-electron cloud.

Of the substituted dihydropyrenes prepared thus far, the internal substituents have been either hydrogen or saturated alkyl groups.[1] Although it has long been of interest to examine the properties of molecules having functionality within the cavity of an aromatic π-electron cloud, the attainment of this objective has been thwarted by certain practical difficulties. The reaction conditions employed in the standard thiacyclophane syntheses of dihydropyrenes are such that only certain types of functionality will survive these conditions unchanged. Secondly, the 1,2,3-trisubstitution pattern needed for such thiacyclophane precursors is an awkward one to provide synthetically, particularly if functionality is to be preserved. We now describe a convenient method for preparing 1,2,3-trisubstituted benzene derivatives and the employment of these precursors for syntheses of dihydropyrenes with internal substituents having vinyl and ether functional groups.

Recently, we reported a synthesis of *trans*-15-*n*-butyl-16-methyldihydropyrene in which a bis(oxazoline) derived from isophthalic acid was used to provide the 1,2,3-trisubstitution pattern through ortho lithiation.[2] Unfortunately, the removal of the oxazoline rings after alkylation requires a rather vigorous acidic hydrolysis, and under these conditions vinyl groups underwent undesired hydration and/or lactonization. To circumvent this, we examined other groups that have been used to direct ortho lithiation.

Corey and Enders have used *N,N*-dimethylhydrazones as protecting and directing groups for α-lithiation of aliphatic carbonyl derivatives.[3] When the bis(*N,N*-dimethylhydrazone) of isophthalaldehyde (**1**) was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and the resulting anion was alkylated with methyl iodide, 2,6-dicyanotoluene (**2**) was isolated in 54% yield (Scheme I). It seemed likely that the conversion of the *N,N*-dimethylhydrazone group to a cyano group was simply a base-catalyzed elimination of dimethylamine. In support of this it was found that treatment of the bis(*N,N*-dimethylhydrazone) of 2-methylisophthalaldehyde (**3**) with LDA followed by addition of deuterium oxide gave in high yield 2,6-dicyano-α-deuteriotoluene (**4**). On the other hand, treatment of the anion of **3** with methyl iodide gave 2,6-dicyanoethylbenzene (**5**) in 81% yield. That the *N,N*-dimethylhydrazone group served no useful purpose,

Scheme I



(1) Boekelheide, V. *Top. Nonbenzenoid Aromat. Chem.* **1973**, *1*, 47.
(2) Harris, T. D.; Neuschwander, B.; Boekelheide, V. *J. Org. Chem.* **1978**, *43*, 727.
(3) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3.

0022-3263/80/1945-2746$01.00/0