= 5.5 Hz), 5.33 (2 H, q, ethyl), 8.62 (3 H, t, ethyl); ^{13}C NMR (20 MHz, $CDCl_3$) 171.96 (CO of $COCF_3$) (J_{C-F} = 34 Hz), 152.07 (CO of COOEt), 137.49, 136.68, 134.05, 131.03 (q, J_{C-F} = 4 Hz), 129.93, 118.09 (q, CF_3, J_{C-F} = 291 Hz), 112.65, 107.81, 105.00, 66.91, 13.60 ppm; λ_{max} (C_6H_{14}) 227 nm (ϵ 13 800), 263 (7900), 312 (18 700), 334 (sh) (9580), 440 (sh) (770); *m/e* 285 ($P,^+$ 19.8%); ν_{CO} (neat) 1800 ($COCF_3$), 1650 cm^{-1} (COOEt)).

The combined spectrochemical information now available on **1** firmly establishes the molecule as "aromatic" and one might ask what is it that desensitizes the 1-pyrindine frame to the known electronic effects of N-substitution. One possible explanation, of course, is that, being topologically constrained to a rigidly flat geometry, a molecule such as **1** may be expected to convert efficiently whatever mobility is available to its lone pair into aromatically stabilizing π delocalization. The situation thus sharply differs from that encountered in the heteronin family where the lone pair must expend a significant portion of its available energy to flatten the system's inherently buckled skeleton. In other words, delocalization in the 1-pyrindine system is expected to be energetically more economical than in the corresponding heteronin and thus to be readily triggered by a relatively low-lying lone pair such as that of the urethane group.

To conclude, it is perhaps worth noting that the loss of symmetry experienced by the 10-π system on passing from planar heteronin (C_{2v}) to 1-pyrindine (C_s) may also be a factor contributing to the greater ease with which the bicyclic variant is known to mobilize low-lying lone pairs. In brief, the absence of nontrivial molecular symmetry in the 1-pyrindine system may be shown to generate a situation whereby all of the system's filled HMOs (ψ_1 to ψ_5) are associated with a certain fraction of lone-pair density, whereas this is not the case with the more symmetrical heteronin system where two of the five filled MOs, including the key HFMO, are found to be entirely devoid of lone-pair density in the simple Hückel approximation. While admittedly approximate, this finding, i.e., that lone-pair density is more evenly distributed among the filled MOs of the bicyclic frame, may be deemed indicative of the system's pronounced affinity for lone-pair delocalization.

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References and Notes

(1) A. G. Anastassiou, S. W. Eachus, R. P. Cellura, and J. H. Gebrian, *Chem. Commun.*, 1133 (1970).
(2) For a review on the subject, see A. G. Anastassiou, *Acc. Chem. Res.*, **5**, 281 (1972).
(3) A. G. Anastassiou, R. L. Elliott, and E. Reichmanis, *J. Am. Chem. Soc.*, **96** 7823 (1974).
(4) For a review on the subject, see A. G. Anastassiou, *Acc. Chem. Res.*, **9**, 453 (1976).
(5) A. G. Anastassiou, S. J. Girgenti, R. C. Griffith, and E. Reichmanis, *J. Org. Chem.*, **42**, 2651 (1977).
(6) A. G. Anastassiou and J. H. Gebrian, *J. Am. Chem. Soc.*, **91**, 4011 (1969); *Tetrahedron Lett.*, 5239 (1969).
(7) This substance appears to be the only member of the 1-pyrindine family to have been reported previously: A. G. Anderson, Jr., and H. L. Ammon, *Tetrahedron*, **23**, 3601 (1967) (see also C. B. Reese, *J. Am. Chem. Soc.*, **84**, 3979 (1962)). The UV–vis absorption spectrum described for a pure sample of this molecule closely corresponds to that of our specimen.
(8) Separation of the mixture was accomplished by column chromatography at −15 °C; the desired substance was further purified by (a) distillation, (b) recrystallization.
(9) *S'* denotes the ratio *S*(X)/*S*(benzene), where *S* is defined by the ratio $[\tau(X) - \tau(C_6H_{12})]/60$ and where τ(X) is the difference in chemical shift between cyclohexane and acetonitrile in solvent X and $\tau(C_6H_{12})$ is the analogous difference in cyclohexane solvent, as developed by F. A. L. Anet and G. E. Schenck, *J. Am. Chem. Soc.*, **93**, 556 (1971). In the present study all *S* values were determined in 1,5-cyclooctadiene (COD) at the prescribed molar concentration of 1 part compound X to 12.4 parts COD.
(10) We are grateful to Professor V. Sniekus for recommending the procedure employed in the synthesis of **8**; see D. J. Harris and V. Snieckus, *J. Chem. Soc., Chem. Commun.*, 844 (1976).
(11) The elemental composition of this substance was established by combustion analysis.
(12) The shielding experienced by the protons attached to the five-membered moiety of the 1-pyrindinelyl anion relative to their counterparts in **1** and **6** is consistent with major contribution by the form shown in **5**.
(13) C. Weizmann, postdoctoral fellow.

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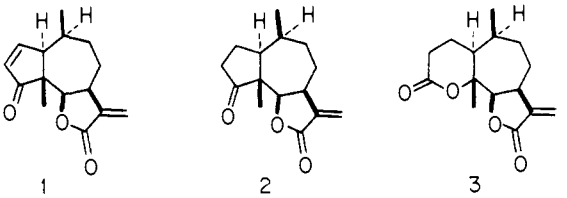
Pseudoguaianolides. Stereospecific Total Synthesis of (±)-Ambrosin, (±)-Damsin, and (±)-Psilostachyin C

Sir:

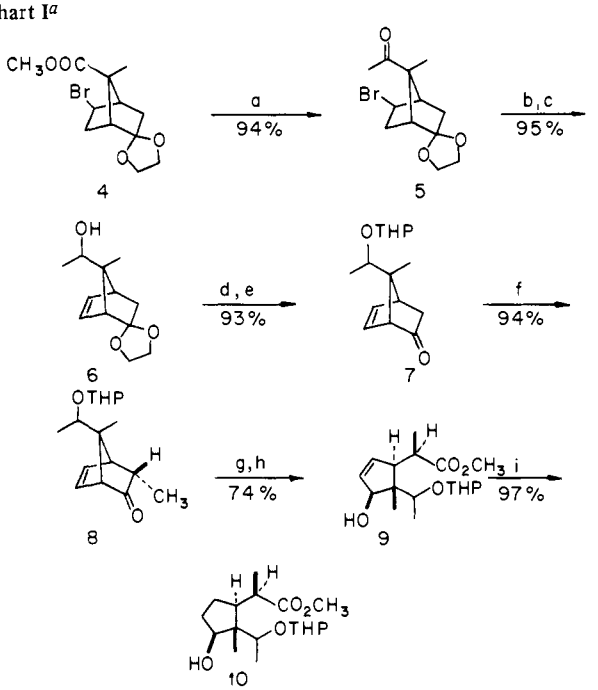
The pseudoguaianolides constitute a family of sesquiterpene lactones possessing a vast array of functional groups about a flexible hydroazulene ring system.[1] Despite the many synthetic approaches to pseudoguaianolides,[2] only two successful syntheses have been recorded.[3,4] We wish to describe the total synthesis of (±)-ambrosin (**1**),[5] (±)-damsin (**2**),[6] and (±)-psilostachyin C (**3**)[7] while maintaining complete stereochemical control during introduction of the five contiguous chiral centers located on the cycloheptane ring. The approach is applicable to a wide range of pseudoguaianolides.



1 2 3

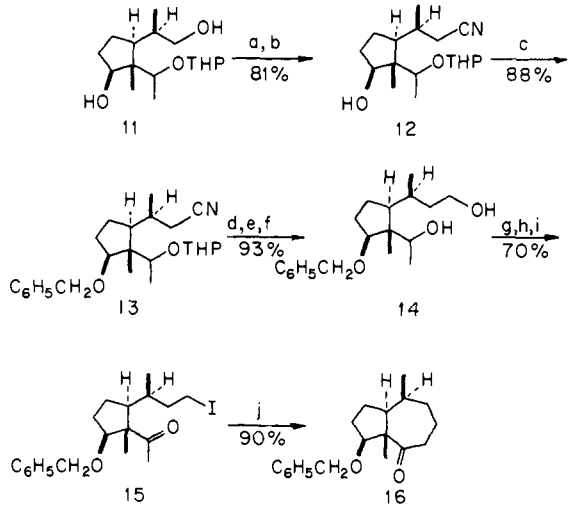
The synthesis of (±)-damsin detailed below was performed in three stages: (a) initial construction of the key cyclopenta-

Chart I[a]



[a] a, MeLi, Et_2O; b, DBU, xylene, reflux; c, $LiAlH_4$, THF, reflux; d, 30% aqueous HOAc, 90 °C; e, DHP, CH_2Cl_2, TsOH; f, LDA, THF, MeI, 0 °C; g, H_2O_2, OH^-, MeOH; h, CH_2N_2; i, H_2, PtO_2, EtOAc.

Chart II[a]



[a] a, TsCl, Py; b, NaCN, Me_2SO; c, NaH, THF, $PhCH_2Br$, HMPA, Bu_4NI, reflux; d, *i*-Bu_2AlH, $PhCH_3$, −78 °C; e, $NaBH_4$, EtOH, 0 °C; f, MeOH, TsOH; g, TsCl, Py; h, Jones reagent; i, NaI, acetone; j, $LiN(SiMe_3)_2$, THF, HMPA, −78 °C (30 min) → −20 °C (2 h).

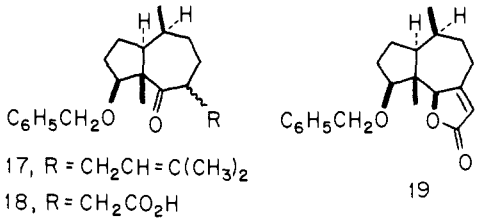
noid intermediate **10** (Chart I), (b) formation of the hydroazulene AB ring system (Chart II), and (c) introduction of the ring C α-methylene-γ-butyrolactone functionality.

Bromo ester **4,** readily available from norbornadiene[8] in high yield, was converted (94%) to methyl ketone **5,** mp 69–70 °C, using methyllithium in ether.[9] Dehydrobromination of **5** with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in refluxing xylene followed by reduction gave alcohol **6** in 95% yield. Deketalization (30% aqueous acetic acid, 90 °C) and tetrahydropyranylation afforded bicyclo[2.2.1]heptenone (**7**). Endo-alkylation of ketone **7** was accomplished exclusively in 94% yield, as expected, with methyl iodide using lithium diisopropylamide in tetrahydrofuran (0 °C). Baeyer–Villiger oxidation[10] of **8** employing hydrogen peroxide and sodium hydroxide in aqueous methanol gave, after esterification, a 74% isolated yield of cyclopentene **9**.[11] Catalytic hydrogenation of the carbon–carbon double bond in **9** using platinum oxide in scrupulously dried ethyl acetate gave a 97% yield of the key intermediate **10**.[12]

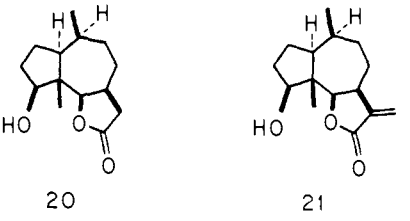
Having assembled three of the five chiral centers of damsin, we focused our attention on ring closure to the required hydroazulene ring system. Prior to ring closure a one-carbon homologation was required (cf. **11** → **15**). Using a standard series of transformations, diol **11,** obtained in 95% yield by reduction (lithium aluminum hydride, ether) of ester **10,** was selectively monotosylated and treated with sodium cyanide in dimethyl sulfoxide. The resulting hydroxy nitrile **12** was conveniently converted in 88% yield to its benzyl ether **13** employing sodium hydride and benzyl bromide in tetrahydrofuran containing hexamethylphosphoramide and tetrabutylammonium iodide (0.4 equiv).[13] In the absence of tetrabutylammonium iodide only a very low yield of **13** was realized.

As illustrated in Chart II nitrile **13** was efficiently converted to diol **14** in very high overall yield. Conversion of diol **14** into keto iodide **15** was accomplished via the following sequence of reactions: (a) selective monotosylation, (b) Jones oxidation, and (c) displacement of the tosylate by iodide. The required ring closure to the hydroazulene system was efficiently carried out via a 7-endo-alkylation[14] in 90% yield upon treatment of keto iodide **15** with lithium bis(trimethylsilyl)amide in anhydrous tetrahydrofuran containing 1.0 equiv of hexamethylphosphoramide (HMPA) at −20 °C.

With hydroazulene **16** (IR (CCl_4) 1695 cm^{-1}; 250-MHz NMR (CCl_4) δ 1.02 (d, 3 H, J = 6.8 Hz), 1.18 (s, 3 H), 4.05 (t, 1 H, J = 6.5 Hz), 4.35 (AB q, 2 H, J = 12.6 Hz, $\Delta\nu_{AB}$ = 23.1 Hz), 7.20 (s, 5 H)) in hand we turned our attention to the construction of the β-oriented α-methylene-γ-butyrolactone unit. Hydroazulene **16** was alkylated (87%) with prenyl bromide using lithium diisopropylamide in tetrahydrofuran containing HMPA (1.0 equiv). Cleavage of the prenyl double bond of **17** was carried out in a straightforward manner with ozone providing, after Jones oxidation, the keto carboxylic acid **18** (88%). Treatment of keto acid **18** with sodium acetate–acetic



anhydride at 140 °C for ~2 h[15] gave as the only isolated product (87%) butenolide **19:** mp 82–83 °C; IR (CCl_4) 1762, 1634 cm^{-1}; NMR (CCl_4) δ 0.74 (s, 3 H), 0.97 (d, 3 H, J = 6.5 Hz), 3.75 (m, 1 H), 4.52 (AB q, 2 H, J = 12 Hz, $\Delta\nu_{AB}$ = 7.2 Hz), 5.62 (s, 1 H), 7.21 (s, 5 H). Hydrogenation of the butenolide double bond (H_2, 5% Pd/C, 0.05 N HCl, 2:1 ethyl acetate–ethanol) was accompanied by debenzylation and gave the cis-fused tricyclic lactone **20** (80%) (IR (CCl_4) 3610, 1790 cm^{-1}; NMR (CCl_4) δ 0.95 (s, 3 H), 1.06 (d, 3 H, J = 7 Hz),



3.90 (m, 1 H), 4.30 (d, 1 H, J = 9 Hz)) possessing the five continuous chiral centers of damsin.

Introduction of the α-methylene unit was carried out *directly on the unprotected hydroxy lactone* **20** in 66% overall yield via the following sequence of reactions: hydroxymethylation, mesylation, and β-elimination (DBU, benzene, 25 °C, 45 min).[16] The methylenated adduct **21** (mp 114–116 °C; IR (CCl_4) 3600, 1780 cm^{-1}; NMR (CCl_4) δ 0.80 (s, 3 H), 1.02 (d, 3 H, J = 6.5 Hz), 3.91 (m, 1 H), 4.40 (d, 1 H, J = 9 Hz), 5.01 (d, 1 H, J = 3.5 Hz), 6.07 (d, 1 H, J = 3.5 Hz)) was smoothly converted (90%) to (±)-damsin (**2**), mp 124–125 °C (lit.[3] 124–126 °C) via oxidation with Jones reagent. The IR and NMR (250 MHz) spectra of synthetic damsin were identical with those of natural damsin.

The preparation of (±)-ambrosin (**1**) was made possible when it was found that introduction of the α-phenylseleno group[17] could be carried out directly on (±)-damsin (**2**) in ethyl acetate containing phenylselenenyl chloride (1.0 equiv) *in the absence of any base.* Oxidation of the product with aqueous sodium periodate (3.0 equiv) in *tert*-butyl alcohol gave a 41% overall yield of (±)-ambrosin, mp 188–190 °C, identical with an authentic sample of natural ambrosin by comparison of spectral properties (IR, NMR) and thin-layer mobility in several solvent systems.

The synthesis of (±)-psilostachyin C (**3**) was carried out by direct Baeyer–Villiger oxidation employing benzeneperoxyseleninic acid[18] generated from benzeneseleninic acid(2.0 equiv) and 30% aqueous hydrogen peroxide (15 equiv) in *tert*-butyl alcohol. (±)-Psilostachyin C, mp 192–193 °C, thus obtained (55%)[19] was identical in all respects with an authentic sample of natural material.

Acknowledgment. This investigation was supported by a

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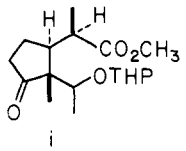
References and Notes

(1) H. Yoshioka, T. J. Mabry, and B. N. Timmermann, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo, 1973.
(2) For a review of synthetic approaches to hydroazulenes, see J. A. Marshall, *Synthesis*, 517 (1972).
(3) For the synthesis of (±)-damsin, see R. A. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976).
(4) For the synthesis of (±)-confertin, see J. A. Marshall and R. H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976).
(5) H. Abu-Shady and T. D. Soine, *J. Am. Pharm. Assoc.*, **42**, 387 (1953); **43**, 365 (1954). W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962); M. T. Emerson, W. Herz, C. N. Caughlan, and R. W. Withers, *Tetrahedron Lett.*, 6151 (1966).
(6) M. Suchy, V. Herout, and F. Sorm, *Collect. Czech. Commun.*, **28**, 2257 (1963); R. W. Doskotch and C. D. Hufford, *J. Pharm. Sci.*, **58**, 186 (1969); K.-H. Lee, E.-S. Huang, C. Piantadosi, J. S. Pagno, and T. A. Geissman, *Cancer Res.*, **31**, 1649 (1971).
(7) H. B. Kagan, H. E. Miller, W. Renold, M. V. Lakshimkantham, L. R. Tether, W. Herz, and T. H. Mabry, *J. Org. Chem.*, **31**, 1639 (1966).
(8) P. A. Grieco and Y. Masaki, *J. Org. Chem.*, **40**, 150 (1975), P. A. Grieco, et al., *J. Am. Chem. Soc.*, **99**, 4111 (1977), and references cited therein.
(9) The NMR and IR spectra for all compounds were in complete accord with their assigned structures. Satisfactory analytical data were obtained for all compounds. NMR spectra were recorded at 60 MHz unless indicated otherwise.
(10) N. M. Weinshenker and R. Stephenson, *J. Org. Chem.*, **37**, 3741 (1972).
(11) The starting ketone **6** was recovered in 24% yield.
(12) During the reduction of **9** in reagent grade ethyl acetate a 20–25% yield of ketone i was observed in addition to compound **10.**



i

(13) S. Czernecki, C. Georgoulis, and C. Provelenghiou, *Tetrahedron Lett.*, 3535 (1976).
(14) J. E. Baldwin and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 233 (1977).
(15) Marshall has employed a similar sequence of reactions in the total synthesis of (±)-4-deoxydamsin: J. A. Marshall and W. R. Snyder, *J. Org. Chem.*, **40**, 1656 (1975).
(16) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972); P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).
(17) H. J. Reich, J. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, **95**, 6137 (1973).
(18) P. A. Grieco, Y. Yokoyama, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **42**, 2034 (1977).
(19) A 20% yield of the corresponding hydroxycarboxylic acid which resulted from hydrolysis of the δ-lactone during the course of the reaction was isolated.
(20) Fellow of the Alfred P. Sloan Foundation.

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Catalytic Homogeneous Hydrogenation of Arenes. 5.[1] The η^6-$C_6(CH_3)_6Ru$-η^4-$C_6(CH_3)_6$ Catalyst

Sir:

The pervasive cis stereochemistry of hydrogen addition to aromatic hydrocarbons elicited by the homogeneous η^3-$C_3H_5CoL_3$ (L = phosphite or phosphine) catalysts and the remarkable selectivity of these catalysts to arenes with respect to alkenes clearly have established the possibility of very selective and stereoselective catalysts for arene hydrogenation.[1-4] Unfortunately, the allylcobalt catalysts fail in a practical sense because of their relatively short lifetimes.[4] An intermediate postulated[3] in the cobalt system, η^1-$C_3H_5CoH_2$-$[P(OCH_3)_3](\eta^4$-$C_6H_6)$, as well as alternative η^6-C_6H_6-cobalt species have raised substantive questions about the susceptibility of π-bonded arenes to hydrogenation.[5-8] From a general investigation of metal arene complexes, we have now obtained fundamental mechanistic information about arene hydrogenation, demonstrated the hydrogenation of an η^6-arene-metal complex, and discovered a new homogeneous and long-lived arene hydrogenation catalyst system.

Hexahapto bonded arenes can be hydrogenated to cyclohexanes. η^6-$CH_3C_6H_5$-$Ru_6C(CO)_{14}$, which is thermally stable and does not undergo arene exchange with a benzene solvent at 150 °C, reacted with hydrogen at 150 °C (2–3 atm) to produce methylcyclohexane quantitatively, a black mirror that appeared to be ruthenium metal, and no recoverable toluene. The reaction effected with benzene as the solvent produced only traces of cyclohexane; the cyclohexane was produced by a ruthenium metal (formed in the initial hydrogenation reaction) catalyzed reaction. Although this reaction system was not catalytic, it does establish for the first time that η^6-arene-metal complexes can be hydrogenated. Attempts to stabilize this reaction system for a catalytic mode by addition of carbon monoxide led to complete suppression of the hydrogenation reaction suggesting that intermediates of the type arene-$Ru_6C(CO)_x$ with $x < 14$ are involved in the hydrogenation.[9] In sharp contrast, $(\eta^6$-$C_6H_6)_2Cr$ and $(\eta^6$-$CH_3C_6H_5)_2Mo$ underwent no hydrogenation in benzene solution at 150 °C (~5 atm). Under these conditions, there was no detectable arene exchange with the benzene solvent in the molybdenum system. Similarly, the η^6-$CH_3C_6H_5M(CO)_3$ (M = Mo, W) complexes were fully resistant to hydrogenation to 120 °C and arene exchange was observed only for the molybdenum complex at 120 °C. At 150 °C, there was gross thermal decomposition and no hydrogenation of the molybdenum carbonyl complex and arene exchange but no hydrogenation of the tungsten analogue.[10]

Of special interest to us has been the arene complexes in which an arene is *tetrahapto* bonded to a metal as in the presumed allylcobalt intermediates.[2] Within this class, the η^6-$C_6(CH_3)_6Ru$-η^4-$C_6(CH_3)_6$[11] complex proved to be a long-lived homogeneous catalyst for the hydrogenation of arenes with turnover rates of ~1/12 min at 90 °C (2–3 atm) for benzene. The reaction solution was clear orange to orange-red. No free hexamethylbenzene was detected in the reaction residues and the ruthenium catalyst was recovered quantitatively after 10-h reaction periods. Hydrogenation rates decreased with increased alkyl substitution on the arene as was observed for the allylcobalt catalyst. Hexamethylbenzene was not hydrogenated;[12] thus, the ruthenium catalyst has no reducible ligand, a critical element for a long-lived catalyst.

There are important differences as well as similarities between the ruthenium and allylcobalt systems. The exceptional cis character of the hydrogen additions in the cobalt catalyst is not present in the ruthenium catalyst where cis to trans ratios in the dimethylcyclohexanes produced from *o*- and *p*-xylenes were 9:1 and 9:2, respectively. These ratios more closely approximate reported stereochemistries with solid state, metallic catalysts. Cyclohexenes were significant products; the percentage of cyclohexenes in the total hydrogenation product were ~5, 40, and 55% for benzene? *o*-xylene, and *p*-xylene, respectively, whereas none is produced from these arenes with the allylcobalt catalyst[1-4] nor with Maitlis' $\{Rh[\eta^5$-$C_5(CH_3)_5]Cl_2\}_2$ catalyst.

The most dramatic distinguishing feature between the ruthenium and allylcobalt catalysts was the verv extensive H-D exchange observed for the former catalyst in arene-D_2 and perdeuterioarene-H_2 reactions. Cyclohexanes from d_0 through