under argon atmosphere for 4 h. The inorganic solid was filtered off and washed with $CHCl_3$, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed with 1 N NaOH and H_2O, dried, and evaporated to give 50 mg of a semicrystalline residue. This residue was chromatographed on alumina basic grade III (CH_2Cl_2) to yield crystalline **10** (37 mg, 70%). An analytical sample was prepared by recrystallization from MeOH: mp 221–223 °C; $[\alpha]^{25}_D$ −112.8° (*c* 0.40, $CHCl_3$); MS (EI), *m/e* 285 (M^+); IR (KBr) 1705 (CO) cm^{-1}; NMR (Me_2SO-d_6) δ 7.06 (dd, 1 H, Ar H, *J* = 8, 8 Hz), 6.73 (t, 2 H, Ar H, *J* = 8 Hz), 3.72 (s, 3 H, OCH_3), 2.24 (s, 3 H, NCH_3).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.45; H, 8.40; N, 4.75.

Acknowledgment. We thank Dr. A. E. Jacobson and L. Atwell from our Section for having evaluated the morphinans mentioned in this paper in the hot-plate assay.

Registry No. **1**, 76193-30-1; **2**, 84960-87-2; **3**, 84960-88-3; **4**, 84960-89-4; **5**, 84960-90-7; **6**, 84986-96-9; **7**, 84960-91-8; **8**, 84960-92-9; **9**, 84960-93-0; **10**, 84960-94-1; benzyl bromide, 100-39-0; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.

Synthesis of the Aryltetralin Lignan Skeleton via the Prins Reaction

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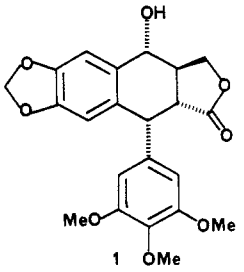
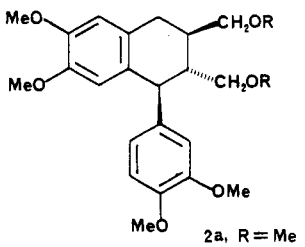
Reaction of a 1,4-diaryl-1-butene (**7**) with paraformaldehyde and the appropriate alkylaluminum halide generates the cation **8**, via addition of formaldehyde to the double bond, which cyclizes to give the aryltetralin **9**. Reaction of 1,4-diphenyl-2-butene (**6a**) with paraformaldehyde and methylaluminum sesquichloride gives the ene adduct **5a**, which reacts further, analogously to **7**, to give **4a** which possesses the aryltetralin lignan skeleton.

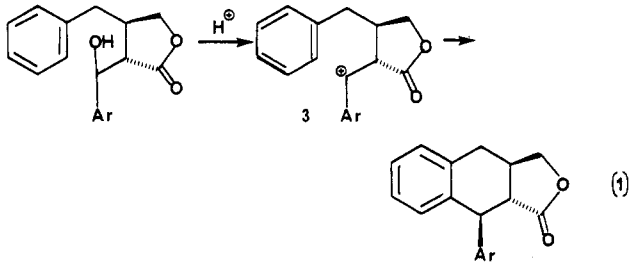
The aryltetralin class of lignans contains a wide variety of compounds including the antitumor agent podophyllotoxin (**1**)[1] and phyltetralin (**2a**).[2] A general route to these





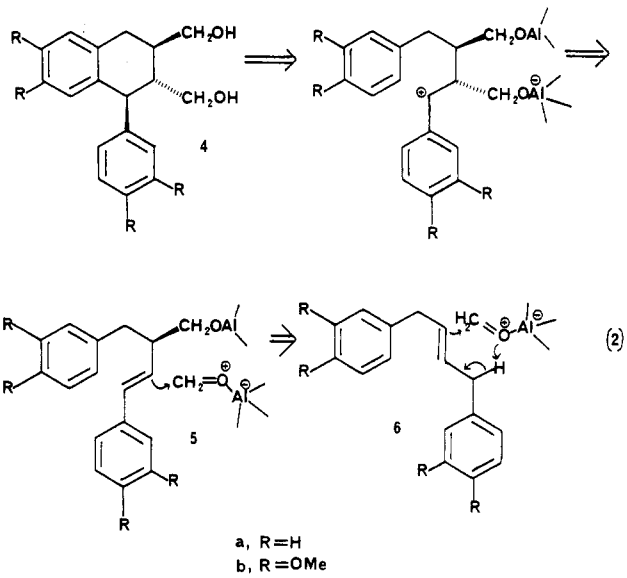
2a, R = Me
2b, R = H

compounds involves the acid-catalyzed cyclization of β-benzyl-α-(hydroxybenzyl)butyrolactones via carbenium ion **3**[2,3] (see eq 1). We were interested in developing alter-



(1)

native routes to these compounds in which carbenium ions analogous to **3** are generated in situ by addition of formaldehyde to the appropriate styrene **5** (see eq 2). This approach is particularly attractive for symmetrical lignans



a, R=H
b, R=OMe

(2)

since the required styrene **5** can itself be constructed in situ from an ene reaction of formaldehyde with 1,4-diaryl-2-butene **6** (see eq 2).

Initial model studies were conducted with 1,4-diaryl-1-butenes (**7**) which are prepared by a Wittig reaction of a dihydrocinnamylphosphonium ylide with a benzaldehyde. Cyclizations to give **9** are carried out in CH_2Cl_2 at 0–20 °C for 30 min with an excess of paraformaldehyde and Lewis acid (see eq 3). The results are summarized in Table I. Good yields of adducts are obtained in all cases except for **7d** and **7f** which contain a methylenedioxy group prone to decomposition during the reaction.[1] The stereochemistry of **9** can be determined by analysis of the NMR spectrum; the doubly benzylic proton of the trans isomer absorbs at δ 3.8–4.0 as a doublet (*J* = 9 Hz) while that of the cis isomer absorbs at δ 4.2–4.4 as a doublet (*J* = 5 Hz).[1]

We have recently shown that alkylaluminum halides are especially effective catalysts for the ene reactions of aldehydes with alkenes since they are proton scavengers as

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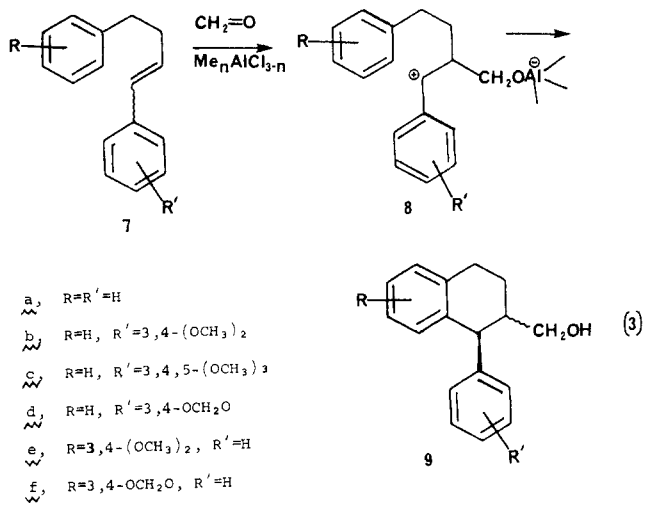

well as Lewis acids.[4] Dimethylaluminum chloride (DMAC) was therefore initially investigated. In some cases it is necessary to use methylaluminum sesquichloride (MASC), which is a more acidic Lewis acid with a less nucleophilic alkyl group, to effect a high degree of conversion to **9**. Use of ethylaluminum dichloride (EADC) gives complex mixtures. The ability to select easily a Lewis acid of appropriate strength is an important advantage of alkylaluminum halides as Lewis acids.

These reactions could proceed through a discrete intermediate **8** or could involve a concerted trans addition to the double bond. Whereas reaction of (*E*)-**7a** gives exclusively *trans*-**9a**, reaction of (*Z*)-**7a** gives a 1:1 mixture of *cis*- and *trans*-**9a**. The reaction therefore has at least a component which proceeds through a cation, **8a**, which, as is well-known,[2,3] cyclizes primarily to the trans isomer. Alkenes **7b** and **7c** give cations which are more stable than **8a** and therefore cyclize more slowly to give a greater percentage of the more stable *trans*-**9**.

Introduction of hydroxymethyl groups at both C-2 and C-3 with cyclization can be carried out in one reaction as indicated in the retrosynthetic scheme (eq 2). Thus treatment of either (*E*)- or (*Z*)-1,4-diphenyl-2-butene (**6a**) with 6 equiv of paraformaldehyde and MASC gives a 40–50% yield of **4a** as the only characterizable product. Since (*E*)-1,4-diphenyl-2-butene is available in one step by the titanium-induced reductive coupling[5] of phenylacetaldehyde, this constitutes a two-step synthesis of the aryltetralin lignan skeleton.

The stereochemistry of **4a** is established by the close similarity of the ^{13}C NMR absorptions of the aliphatic carbons of **4a** and related natural products[6] and confirmed by the coupling constant J_{H_1,H_2} = 10 Hz which is characteristic of *trans*-1,2,*trans*-2,3 lignans.[1] The initial ene reaction will produce ~90% (*E*)-**5a**[4b] which will lead to **4a** with the phenyl and 2-hydroxymethyl groups trans as has been shown in the cyclization of (*E*)-**7a**. The trans relationship between the 2- and 3-hydroxymethyl groups is not required but will result if the 3-hydroxymethyl group adopts a quasiequatorial position in the transition state.

Unfortunately, all attempts to cyclize **6b**, which would provide the phyltetralin precursor **2b**, were unsuccessful. The double bond of **6b** is not very nucleophilic and is apparently further deactivated by complexation of the Lewis acid to the methoxy groups. Although the conversion of **6** to **4** appears to be a method of limited utility, the model studies suggest that conversion of **8** to **9** will be general.

Table I. Reaction of 1,4-Diaryl-1-butene 7 with Formaldehyde

alkene	% E^a	Lewis acid (equiv)	product	% yield	% trans
7a	41	DMAC (3)	9a	90	70
7a	100	DMAC (3)	9a	95	100
7a	0	DMAC (3)	9a	77	50
7b	67	DMAC (3)	9b	88	92
7c	67	MASC (3)	9c	62	100
7d	64	DMAC (3)	9d	38	80
7e	45	MASC (6)	9e	82	75
7f	40	DMAC (3)	9f	25	50

[a] Determined by GC analysis of **7**.

Experimental Section

All reactions involving air- or moisture-sensitive reagents were conducted in anhydrous solvents under nitrogen in flame-dried glassware. DMAC and methylaluminum dichloride (MADC) were obtained from Texas Alkyls as solutions in heptane and hexane, respectively. EADC was obtained from Alfa as a solution in heptane. MASC was prepared by combining equimolar amounts of MADC and DMAC. CH_2Cl_2 and benzene were freshly distilled from CaH_2. THF was distilled from sodium–benzophenone ketyl. DME was distilled from CaH_2, refluxed over potassium for 10 h, and redistilled.

NMR spectra were obtained on Perkin-Elmer R32 or Bruker WH 90 spectrometers. IR spectra were obtained on a Perkin Elmer 683 spectrometer. Gas chromatography was carried out on a 0.25 in. × 12 ft 10% FFAP on Chromosorb WNAW (A) or a 0.25 in. × 10 ft 3% SE-30 on Chromosorb WNAW (B) columns. Elemental analyses were performed by Galbraith Laboratories.

Starting Materials. (3-Phenylpropyl)triphenylphosphonium bromide was prepared by the procedure of Bestmann and Hartung.[7] 3-[3,4-(Methylenedioxy)phenyl]propyl bromide[8] was prepared by reduction of 3,4-(methylenedioxy)cinnamic acid with $LiAlH_4$ in refluxing THF[9] to give 3-[3,4-(methylenedioxy)-phenyl]propanol which was treated with PBr_3 in benzene at 65 °C. 3-[3,4-(Methylenedioxy)phenyl]propyltriphenylphosphonium bromide (mp 201.5–202.5 °C) was prepared by the procedure of Bestmann and Hartung.[7] 3-(3,4-Dimethoxyphenyl)propyl bromide[10] and [3-(3,4-dimethoxyphenyl)propyl]triphenylphosphonium bromide (mp 144.5–146.5 °C) were prepared analogously.

Preparation of 1,4-Diphenyl-1-butene (7a). A suspension of 1.15 g (2.5 mmol) of (3-phenylpropyl)triphenylphosphonium bromide[7] in 10 mL of THF was treated with 1.9 mL of 1.6 M *n*-BuLi in hexane. The resulting solution was stirred for 20 min and treated with 0.32 g (3 mmol) of benzaldehyde in 5 mL of THF. The resulting mixture was stirred for 30 min, poured onto ice, and diluted with ether. The aqueous phase was separated and extracted three times with ether. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give a residue which was extracted with cold hexane. Evaporation of the hexane solution gave 458 mg of crude product. Chromatography on silica gel (hexane) gave 351 mg (67%) of **7a** as a 59:41 *Z*–*E* mixture. The isomers were separated by preparative GC.

The data for (*Z*)-**7a** follow: NMR ($CDCl_3$) δ 6.45 (d, 1, J = 12 Hz), 5.68 (dt, 1, J = 12,7 Hz), 2.72 (br s, 4); GC (A, 225 °C) t_R = 15.8 min.

The data for (*E*)-**7a** follow: NMR ($CDCl_3$) δ 6.2–6.55 (m, 2), 2.35–2.9 (m, 4); GC (A, 225 °C) t_R = 22.3 min.

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The data are consistent with that previously reported.[11]

1-(3,4-Dimethoxyphenyl)-4-phenyl-1-butene (7b) was prepared analogously from 3,4-dimethoxybenzaldehyde. Chromatography of the crude product on silica gel (1:1 hexane–ether) gave 583 mg (87%) of **7b** as a 33:67 *Z–E* mixture: mp (two stages) 30.0–31.5 and 34.5–35.5 °C; NMR ($CDCl_3$) δ 7.25 (s, 5), 6.7–7.0 (m, 3), 5.5–6.6 (m, 2), 3.86 (s, 3), 3.84 (s, 3), 2.3–3.0 (m, 4); IR (KBr) 2930, 1608, 1584, 1519, 1458, 1271, 1248, 1164, 1145, 1033, 712 cm^{-1}; GC (B, 225 °C) t_R = 15.2 (*Z*), 21.0 min (*E*). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.46; H, 7.81.

1-(3,4,5-Trimethoxyphenyl)-4-phenyl-1-butene (7c) was prepared analogously from 3,4,5-trimethoxybenzaldehyde. Chromatography of the crude product on silica gel (1:1 hexane–ether) gave 644 mg (87%) of **7c** as a 33:67 *Z–E* mixture: NMR ($CDCl_3$) δ 7.25 (s, 5), 6.57 (s, 2), 5.5–6.5 (m, 2), 3.86 (s, 6), 3.84 (s, 3), 2.3–3.0 (m, 4); IR (neat) 2930, 1583, 1510, 1457, 1420, 1334, 1243, 1132, 1017, 809 cm^{-1}; GC (B, 225 °C) t_R = 23.7 (*Z*), 34.5 min (*E*). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.26; H, 7.37.

1-[3,4-(Methylenedioxy)phenyl]-4-phenyl-1-butene (7d) was prepared analogously from piperonal. Chromatography of the crude product on silica gel (9:1 hexane–ether) gave 458 mg (73%) of **7d** which was further purified by evaporative distillation (120 °C, 0.05 torr) to give 410 mg (65%) of pure **7d** as a 36:64 *Z–E* mixture: NMR ($CDCl_3$) δ 7.24 (s, 5), 6.90 (s, 1), 6.74 (s, 2), 5.90 (s, 2), 5.45–6.5 (m, 2), 2.3–2.9 (m, 4); GC (B, 225 °C) t_R = 15.6 (*Z*), 20.8 min (*E*). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.09; H, 6.54.

4-(3,4-Dimethoxyphenyl)-1-phenyl-1-butene (7e) was prepared analogously from [3-(3,4-dimethoxyphenyl)propyl]triphenylphosphonium bromide and benzaldehyde. Chromatography of the crude product on silica gel (1:1 hexane–ether) gave 535 mg (80%) of **7e** as a 55:45 *Z–E* mixture: NMR ($CDCl_3$) δ 7.11 (br s, 5), 6.60 (br s, 3), 5.89–6.46 (m, 0.45 × 2 + 0.55), 5.29–5.83 (m, 0.55), 3.66 (s, 6), 2.16–2.77 (m, 4); GC (B, 225 °C) t_R = 18.7 (*Z*), 23.2 min (*E*). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.66.

4-[3,4-(Methylenedioxy)phenyl]-1-phenyl-1-butene (7f) was prepared analogously from [3-[3,4-(methylenedioxy)phenyl]-propyl]triphenylphosphonium bromide and benzaldehyde. Chromatography of the crude product on silica gel (9:1 hexane–ether) gave 165 mg (65%) of **7f** as a 60:40 *Z–E* mixture: NMR ($CDCl_3$) δ 7.26 (br s, 5), 6.48–6.85 (m, 3), 5.87 (s, 2), 5.5–6.45 (m, 2), 2.37–2.86 (m, 4); GC (B, 220 °C) t_R = 16.9 (*Z*), 21.2 min (*E*). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.34. Found: C, 81.02; H, 6.46.

(*Z*)-1,4-Diphenyl-2-butene ((*Z*)-6) was prepared by a modification of the procedure of Lambert and co-workers.[12] The phosphonium salt was generated in situ and treated with THF and then BuLi to generate the phosphorane.

(*E*)-1,4-Diphenyl-2-butene ((*E*)-6). A stirred slurry of $TiCl_3$ (1.9 g, 12 mmol) and Zn–Cu couple (1.8 g, 27.7 mmol) in DME (30 mL) was heated at reflux for 1 h.[5] Phenylacetaldehyde (0.36 g, 3 mmol) in DME (5 mL) was added to the cooled mixture which was then heated at reflux for 16 h. The cooled mixture was diluted with ether and filtered with suction through Florisil. Evaporation of the filtrate in vacuo gave 213 mg of crude product. Evaporative distillation (102 °C, 0.1 torr) of 184 mg of the product gave 63 mg (23%) of **6a** as a 90:10 *E–Z* mixture: NMR ($CDCl_3$) δ 7.21 (br s, 10), 5.66 (m, 2), 3.39 (m, 4); GC (A, 225 °C) t_R = 18.9 (*E*), 20.5 min (*Z*).

Cyclization of (*E*)-7a. DMAC (0.29 mL of a 1.14 M solution in heptane, 0.33 mmol) was added to a stirred suspension of paraformaldehyde (10 mg, 0.33 mmol) in a solution of (*E*)-**7a** (22 mg, 0.11 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The solution was allowed to warm to 20 °C, stirred for 1 h, and quenched by addition of water and ether. The aqueous phase was separated and extracted twice with ether. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give 25 mg (95%) of *trans*-**9a** as white crystals: NMR ($CDCl_3$) δ 6.8–7.5 (m, 10), 3.90 (d, 1, *J* = 9 Hz), 3.63 (dd, 1, *J* = 5, 11 Hz), 3.42 (dd, 1, *J* = 5, 11 Hz), 2.85–3.10 (m, 2), 1.4–2.3 (m, 4); IR (KBr) 3320, 2920, 2885, 1499, 1457, 1080, 1056, 1042, 763, 757, 716 cm^{-1}. An analytical sample was prepared by recrystallization from pentane: mp 93–93.5 °C. Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.43; H, 7.72.

Cyclization of (*Z*)-7a (40 mg, 0.19 mmol) under analogous conditions gave 35 mg (77%) of crude product which was shown by NMR to be a 1:1 mixture of *trans*- and *cis*-**9a**: NMR ($CDCl_3$) δ 4.36 (d, 0.5 × 1, *J* = 6 Hz, cis), 3.90 (d, 0.5 × 1, *J* = 9 Hz, trans).

Cyclization of 7b. DMAC (1.25 mL of a 1.14 M solution in heptane, 1.41 mmol) was added to a stirred suspension of paraformaldehyde (42 mg, 1.41 mmol) in a solution of **7b** (67% *E*, 125 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The solution was warmed to 20 °C, stirred for 0.5 h, and quenched with water. The mixture was filtered with suction through Celite. The aqueous layer was separated and extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo to give 182 mg of crude product. Chromatography on silica gel (ether) gave 131 mg (88%) of **9b** which was ca. 92% trans by NMR. Crystallization from pentane gave pure *trans*-**9b**: mp 61.5–63.5 °C; NMR ($CDCl_3$) δ 6.6–7.2 (m, 7), 3.82 (s, 3), 3.77 (s, 3), 3.61 (dd, 1, *J* = 6, 12 Hz), 3.45 (dd, 1, *J* = 4, 12 Hz), 2.85–3.1 (m, 2), 1.5–2.3 (m, 4) (the doubly benzylic proton is obscured by the methoxy groups); IR (KBr) 3090–3630, 2925, 1518, 1257, 1240, 1148, 1032, 755 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.31; H, 7.54.

Cyclization of 7c (67% *E*, 109 mg, 0.37 mmol) was carried out analogously, except that MASC (0.85 mL of a 1.3 M solution in hexane–heptane, 1.11 mmol) was used, to give 110 mg of crude product. Chromatography on silica gel (ether) gave 33 mg of recovered **7c** and 75 mg (62%) of **9c**, which was >95% trans, as an oil which slowly crystallized. Recrystallization from pentane gave 49 mg (40%) of analytically pure *trans*-**9c**: mp 119.5–120 °C; NMR ($CDCl_3$) δ 6.7–7.3 (m, 4), 6.33 (s, 2), 3.84 (s, 3), 3.78 (s, 6), 3.71 (dd, 1, *J* = 9, 12 Hz), 3.47 (dd, 1, *J* = 7,12 Hz), 2.82–3.08 (m, 2), 1.5–2.3 (m, 4) (the doubly benzylic proton is obscured by the methoxy groups); IR (KBr) 3530, 2930, 1591, 1509, 1469, 1427, 1241, 1136, 832, 761 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 72.94; H, 7.33.

Cyclization of 7d (64% *E*, 71 mg, 0.29 mmol) was carried out analogously to that for **7a** to give 67 mg of crude product. Chromatography of 54 mg on silica gel (1:1 hexane–ether) gave 24 mg (38%) of **9d** as an 80:20 trans–cis mixture, which slowly crystallized at 0 °C: NMR ($CDCl_3$) δ 6.94–7.2 (m, 3), 6.64–6.94 (m, 3), 6.56 (s, 1), 5.90 (s, 2), 4.28 (d, 0.2 × 1, *J* = 5 Hz, cis), 3.82 (d, 0.8 × 1, *J* = 9 Hz, trans), 3.69 (dd, 1, *J* = 6, 12 Hz), 3.47 (dd, 1, *J* = 8, 12 Hz), 2.82–3.09 (m, 2), 1.3–2.3 (m, 4); IR (neat) 3080–3620, 2920, 1507, 1490, 1443, 1248, 1048, 944, 819, 754 cm^{-1}. An analytical sample was prepared by recrystallization from pentane: mp 60.0–65.0 °C. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.33; H, 6.69.

Cyclization of 7e (45% *E*, 153 mg, 0.57 mmol) was carried out analogously, except that 6 equiv of paraformaldehyde and MASC (2.4 mL of a 1.4 M solution in hexane–heptane) were used, to give 175 mg of crude product. Chromatography on silica gel (ether) gave 139 mg (82%) of **9e** which was ~75% trans. The isomers were not resolved by TLC. Recrystallization from ether gave 89 mg (52%) of *trans*-**9e**: mp 93–94 °C; NMR ($CDCl_3$) δ 7.0–7.4 (m, 5), 6.61 (s, 1), 6.23 (s, 1), 3.82 (s, 3), 3.55 (s, 3), 3.2–3.8 (m, 3), 2.82 (m, 2), 1.4–2.2 (m, 3); IR (KBr) 3100–3600, 2910, 1519, 1460, 1262, 1229, 1086, 1047, 878, 758, 713 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.67; H, 7.69.

The data for *cis*-**9e** were determined from the mixture: NMR ($CDCl_3$) δ 6.66 (s, 1), 6.39 (s, 1), 4.24 (d, *J* = 5 Hz, 1), 3.82 (s, 3), 3.63 (s, 3).

Cyclization of 7f (40% *E*, 134 mg, 0.53 mmol) was carried out analogously to that of **7a** to give 97 mg of crude product. Chromatography on silica gel (ether) gave 38 mg (25%) of **9f** as a ca. 1:1 trans–cis mixture: NMR ($CDCl_3$) δ 4.24 (d, 0.5 × 1, *J* = 5 Hz, cis), 3.80 (d, 0.5 × 1, *J* = 8 Hz, trans).

Cyclization of (*Z*)-6a. MASC (2.4 mL of a 1.4 M solution in hexane–heptane, 3.36 mmol) was added to a stirred suspension of paraformaldehyde (103 mg, 3.42 mmol) in a solution of (*Z*)-**6a** (89% pure, 92% *Z*, 118 mg, ca. 0.50 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The solution was allowed to warm to 20 °C, stirred for 0.5 h, and quenched by addition of CH_2Cl_2, water, and 10% hydrochloric acid. The aqueous layer was separated and extracted twice

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with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give 130 mg of an oil. ^{13}C NMR revealed only six signals below δ 100, indicating that only one isomer was formed. Chromatography of the crude product on silica gel (ether) gave 68 mg (51%) of **4a** as a crystalline solid. An analytical sample was prepared by recrystallization from pentane–ether: mp 84.5–85.5 °C; NMR ($CDCl_3$) δ 6.65–7.4 (m, 9),3.94 (d, 1, J = 10 Hz), 3.35–3.9 (m, 4), 2.85 (m, 2), 1.7–2.2 (m, 2); ^{13}C NMR ($CDCl_3$) δ 66.0, 62.4, 48.4, 48.0 39.6, 33.5; IR (KBr) 3270, 2900, 1077, 1064, 1031, 968, 756, 713 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.35; H, 7.76.

Cyclization of (*E*)-6a (90% *E*, 48 mg, 0.23 mmol) as described above gave 67 mg of crude product. Chromatography of this on silica gel (ether) gave 5 mg (41%) of pure **4a** identical with that obtained from (*Z*)-**6a**.

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Registry No. **4a**, 85185-48-4; (*Z*)-**6**, 1142-21-8; (*E*)-**6**, 1142-22-9; (*Z*)-**7a**, 70388-65-7; (*E*)-**7a**, 27066-35-9; (*Z*)-**7b**, 85185-27-9; (*E*)-**7b**, 85185-28-0; (*Z*)-**7c**, 85185-29-1; (*E*)-**7c**, 85185-30-4; (*Z*)-**7d**, 85185-31-5; (*E*)-**7d**, 85185-32-6; (*Z*)-**7e**, 85185-33-7; (*E*)-**7e**, 85185-34-8; (*Z*)-**7f**, 85185-35-9; (*E*)-**7f**, 85185-36-0; *trans*-**9a**, 85185-37-1; *cis*-**9a**, 85185-38-2; *trans*-**9b**, 85185-39-3; *cis*-**9b**, 85185-40-6; *trans*-**9c**, 85185-41-7; *trans*-**9d**, 85185-42-8; *cis*-**9d**, 85185-43-9; *trans*-**9e**, 85185-44-0; *cis*-**9e**, 85185-45-1; *trans*-**9f**, 85185-46-2; *cis*-**9f**, 85185-47-3; 3-[3,4-(methylenedioxy)phenyl]-propyl bromide, 28437-31-2; 3-[3,4-(methylenedioxy)phenyl]-propanol, 7031-03-0; 3-(3,4-dimethoxyphenyl)propyl bromide, 3945-85-5; (3-phenylpropyl)triphenylphosphonium bromide, 7484-37-9; benzaldehyde, 100-52-7; 3,4-dimethoxybenzaldehyde, 120-14-9; 3,4,5-trimethoxybenzaldehyde, 86-81-7; piperonal, 120-57-0; [3-[3,4-(methylenedioxy)phenyl]propyl]triphenyl-phosphonium bromide, 28437-34-5; [3-(3,4-dimethoxyphenyl)-propyl]triphenylphosphonium bromide, 57293-20-6; phenyl-acetaldehyde, 122-78-1.

Metal–Ammonia Reduction of Cycloalkanones. A Revised Mechanism

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Reduction of 9-oxo-α-agarofuran (**2**) with lithium, sodium, or potassium in liquid ammonia in the presence of excess ethanol affords as the almost exclusive product the equatorial 9α-ol (**3**). In the absence of an added proton donor, lithium–ammonia reduction of ketone **2** gives a 1.4 ratio of equatorial to axial alcohol. With sodium the ratio is 0.3 and with potassium 0.2. On the basis of the relative rates of chromate oxidation of alcohol **3** and its axial epimer (**4**), the equatorial alcohol is the more stable isomer. Reduction of 8,8-dideuterio ketone **2** with sodium–ammonia–*tert*-butyl alcohol affords an equatorial–axial ratio of 2.6, compared to 1.2 with the undeuterated substrate. None of the 9α-ol (**3**) produced from the deuterated ketone has deuterium at the carbinol position, while the 9β-ol (**4**) contains 43% deuterium incorporation at this position. On the basis of these data and a survey of the results obtained in the reduction of other cycloalkanones, a revised mechanism is proposed for these reactions.

The mechanism of the metal–ammonia reduction of cycloalkanones and the stereochemical consequences thereof have attracted considerable attention since Barton first suggested that these reductions invariably afford the more stable of a pair of epimeric alcohols via a vicinal dianion.[1] Subsequently it was found that in many instances these reactions afford mixtures rich in the less stable epimeric alcohol, and a stepwise mechanism which has been generally accepted was proposed by House.[2] Recently, however, Rautenstrauch has found that reductions of (+)-[3,3-$^2H_2$]camphor[3] or 2,2-dimethyl[6,6-$^2H_2$]-cyclohexanone[4] by alkali metals in ammonia *in the presence of alcohols* afford products in which substantial amounts of the reduced alcohol contain deuterium at the carbinol carbon, and in the absence of an added proton donor, deuterium transfer is the major reaction path.[3,5]

Rautenstrauch has suggested that these reductions occur via a metal ketyl dimer by transfer of a hydrogen atom from the α-position of one ketyl to the carbinol position of the other within the dimer.[3,4] He also suggests, on the basis of experimental pK_a data for ketyls,[6] that neither alcohols nor ammonia is sufficiently acidic to protonate the radical anion and that the path proposed by House competes ineffectively with the hydrogen-transfer process even in reductions carried out in the presence of alcohols.[3] Also, reduction of (+)-[3,3-$^2H_2$]camphor by alkali metals in ammonia in the presence of ammonium chloride affords little reduction product with deuterium at the carbinol carbon, and Rautenstrauch suggests that the previously accepted House mechanism is operative in this case, and reductions by alkali metals in ammonia carried out in the presence of ammonium chloride will give the thermodynamically more stable of a pair of epimeric alcohols as the major product.[3]

However, in contrast to these generalizations, reduction of norcamphor by alkali metals in liquid ammonia in the presence of ammonium chloride has been reported to afford the less stable endo alcohol as the predominent product,[7] and lithium–ammonia reduction of 2,2-dimethyl[6,6-$^2H_2$]cyclohexanone in the presence of ethanol

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