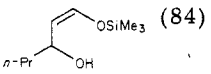
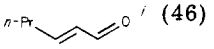
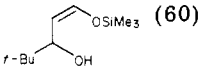
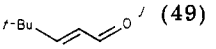
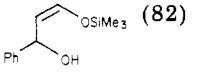
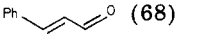
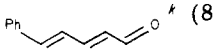
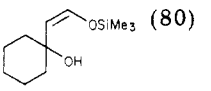
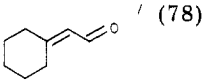
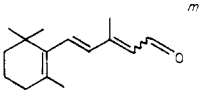
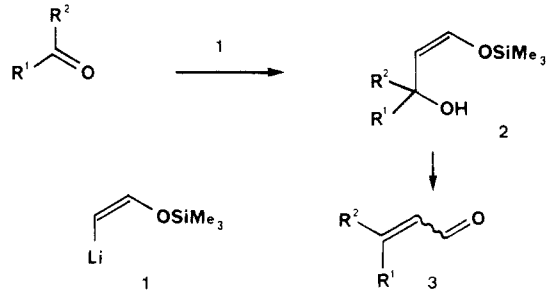
Table I. Reaction of (*Z*)-2-(Trimethylsiloxy)vinyllithium with Aldehydes and Ketones

electrophile	conditions[a]	adduct 2[b,c] (yield, %)[d]	hydrolysis product 3[e,f] (yield, %)[g]
butanal		 (84)	 [i] (46)
2,3-dimethylpropanal		 (60)	 [j] (49)
benzaldehyde		 (82)	 (68)
cinnamaldehyde	30 min, −75 °C		 [k] (86)
cyclohexanone	16 h, −75 °C	 (80)	 [l] (78)
β-ionone	2 h, −50 °C		 [m] (44)[h]

[a] Contact time after addition of the electrophile. [b] Hydrolysis with 5% aqueous Na_2CO_3 solution. [c] Characterized by spectral data. [d] Yields of crude products based upon starting electrophiles. [e] Hydrolysis with hydrochloric acid in THF solution. [f] All products exhibited satisfactory NMR, IR, and mass spectral data. [g] Nonoptimized yields of distilled products, based upon starting electrophiles (intermediate adducts **2** were not isolated). [h] Purified by distillation and chromatography on silica gel. [i] See ref 12. [j] See ref 8d. [k] See ref 11. [l] See ref 8b,c and 13. [m] See ref 5a,b and 14.

Scheme II



Experimental Section

The following experiments illustrate typical procedures.

5-Phenyl-2,4-pentadienal. *tert*-Butyllithium (4 mmol, 2.2 mL, 1.8 M in *n*-pentane) was added dropwise to a solution of (*Z*)-2-bromo-1-(trimethylsiloxy)ethylene (0.43 g, 2.2 mmol) in 15 mL of diethyl ether at −70 °C under dry nitrogen. Following 90 min of stirring at −70 °C (in order to destroy the generated *t*-BuBr), cinnamaldehyde (0.28 g, 2.1 mmol) in 1 mL of diethyl ether was added over a 5-min period. After 30 min at −75 °C, the reaction mixture was allowed to warm to 0–5 °C (20 min). Then, a solution of 2 mL of 1.5 N hydrochloric acid in 10 mL of tetrahydrofuran was added. After an additional 30 min, the reaction mixture was extracted with diethyl ether and distilled [bp 115–120 °C (0.1 mmHg)] to yield 0.29 g (86%) of 5-phenyl-2,4-pentadienal: IR (liquid) 1675, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.25 (dd, *J* = 8, 14.7 Hz, 1), 6.9–7.5 (m, 8), 9.55 (d, *J* = 8 Hz, 1) (see the literature[11] for comparison).

(*Z*)-1-(Trimethylsiloxy)-1-hexen-3-ol. Butanal (1.02 g, 2.1 mmol) in 1 mL of diethyl ether was added to (*Z*)-[2-(trimethylsilyloxy)vinyl]lithium prepared as above. After warming to 0 °C, the reaction mixture was quenched with Na_2CO_3 solution (5%). After the workup, 0.33 g (84% yield) of crude 1-(trimethylsiloxy)-1-hexen-3-ol was obtained: IR (liquid) 3400 (br), 1658 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.20 (d, *J* = 4.7 Hz, 1), 5.35 (m, 1), 4.56 (m, 1), 3.2 (br s, 1, OH exchange with D_2O), 1.90–0.80 (m, 7), 0.20 (s, 9).

(*Z*)-1-(Trimethylsiloxy)-4,4-dimethyl-1-penten-3-ol: IR (liquid) 3450 (br), 1660 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.27 (d, *J* = 6 Hz, 1), 4.60 (dd, *J* = 6, 7.3 Hz, 1), 4.22 (d, *J* = 7.3 Hz, 1), 3.1 (br, s, 1, OH exchange with D_2O), 0.90 (s, 9), 0.20 (s, 9).

(*Z*)-3-(Trimethylsiloxy)-1-phenyl-2-propen-1-ol: IR (liquid) 3490 (br), 1655 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.4–7.35 (m, 5), 6.29 (d, *J* = 6 Hz, 1), 5.73 (d, *J* = 8 Hz, 1), 4.85 (dd, *J* = 6, 8 Hz, 1), 2.75 (br, s, 1, OH exchange with D_2O), 0.20 (s, 9).

1-[(*Z*)-2-(Trimethylsiloxy)vinyl]cyclohexanol: IR (liquid) 3420 (br), 1655 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.05 (d, *J* = 6.7 Hz, 1), 4.53 (d, *J* = 6.7 Hz, 1), 3.7 (br, s, 1, OH exchange with D_2O), 1.5–1.0 (m, 10), 0.15 (s, 9).

Registry No. 1, 78108-48-2; 2 (R¹ = Pr; R² = H), 78108-49-3; 2 (R¹ = *t*-Bu; R² = H), 78108-50-6; 2 (R¹ = Ph; R² = H), 78108-51-7; 2 (R¹ = R² = cyclohexyl), 78108-52-8; 3 (R¹ = Pr; R² = H), 505-57-7; 3 (R¹ = *t*-Bu; R² = H), 926-37-4; 3 (R¹ = C=CHPh; R² = H), 13466-40-5; 3 (R¹ = R² = cyclohexyl), 1713-63-9; 3 (R¹ = CH=CH(2,6,6-trimethyl-1-cyclohexen-1-yl); R² = CH_3), 1209-68-3; butanal, 123-72-8; 2,2-dimethylpropanal, 630-19-3; benzaldehyde, 100-52-7; cinnamaldehyde, 104-55-2; cyclohexanone, 108-94-1; β-ionone, 14901-07-6.

Oxazoline Chemistry. Preparation of Isoquinolines and 2,2′-Bisoxazolines

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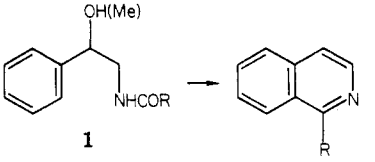
The Pictet–Gams synthesis[1] of fully aromatic isoquinolines (eq 1) via 2-hydroxy(or methoxy)phenethyl-

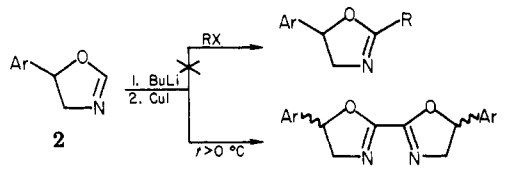


(1)

(1) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74–150.

0022-3263/81/1946-3742$01.25/0

Scheme I



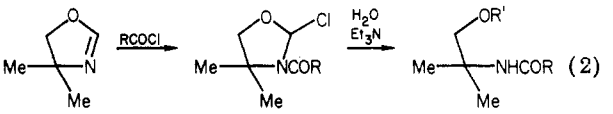
2 3

a, Ar = 3,4-$MeOC_6H_3$; b, Ar = C_6H_5

amide 1 is trammelled by the availability of 1 which is often prepared by multistep syntheses.[2] The current need in our laboratories for a variety of substituted isoquinolines fostered an interest in more efficient alternatives and, in particular, the appplication of 5-aryl-2-oxazolines as chemical templates leading to 1. It has been shown[3] previously that 5-aryl-2-oxazolines undergo facile hydrolysis to 2-hydroxyphenethylformamides (1 R = H) in high yield. In addition, 5-aryl-2-oxazolines can be converted into isoquinolines directly,[4] albeit under somewhat strenuous conditions (P_2O_5 in boiling decalin).

The envisioned route involved alkylation of 5-aryl-2-oxazolines followed by hydrolysis to 1 (R = alkyl) and Pictet–Gams cyclization. Direct alkylation of a 2-oxazoline by conversion to its 2-lithio derivative is unsatisfactory[5,6] due to an unfavorable tautomeric equilibrium[5,7] with the corresponding 2-alkoxyethylisocyanide.[8] We sought to influence the equilibrium by converting the 2-lithio salt to a cuprate and allowing this to couple with reactive alkyl halides.[9] In brief, sequential treatment of **2a** with *n*-butyllithium, cuprous iodide, and either methyl iodide, benzyl bromide, or chloromethyl methyl ether failed to provide useful amounts of C-2 alkylation product at −20 or 0 °C overnight. Above 0 °C, the principal products, in the presence or absence of alkyl halide, were a separable pair of isomeric 2,2′-bisoxazolines **3a**, obtained in ca. 30% and 10% yield after recrystallization (Scheme I).[10] All spectra data and combustion analyses for both isomers are in full accord with the assigned structures, although an unambiguous stereochemical assignment has not been made. Similarly, **2b** gave **3b**. The addition of methyl sulfide and tributylphosphine as stabilizing ligands did not alter the results.

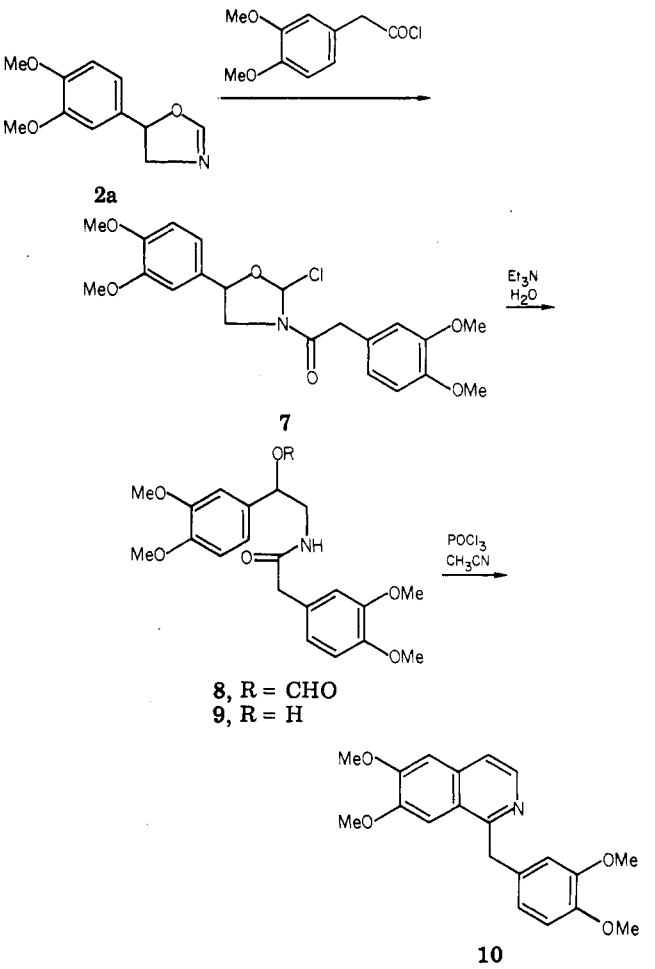
Next, we turned our attention to the report[11] that under carefully defined conditions 2-unsubstituted oxazolines, e.g., 4,4-dimethyl-2-oxazoline (eq 2), react rapidly in



4 5, R′ = H 6, R′ = CHO

CH_2Cl_2 with acyl chlorides to give 1:1 adducts formulated as *N*-acyl-2-chlorooxazolidines **4**, which in turn generate a mixture of **5** and **6** when treated with wet triethylamine. This report, in conjunction with the ready availability of 5-aryl-2-oxazolines from aromatic aldehydes,[6] suggested a new and versatile approach to C-1 substituted isoquinolines.

Scheme II



2a 7 8, R = CHO 9, R = H 10

This route was realized experimentally in a synthesis of the opium constituent papaverine (**10**, Scheme II). Dropwise addition of (3,4-dimethoxyphenyl)acetyl chloride to a dilute CH_2Cl_2 solution of 5-(3,4-dimethoxyphenyl)-2-oxazoline (**2a**) gave[11] adduct **7** which was carefully hydrolyzed in situ with wet triethylamine, affording a 2.2:1 mixture of **8** and **9** as determined by NMR analysis of the crude reaction product. The structure of **8** was confirmed by hydrolysis ($NaHCO_3$) to **9**. Pictet–Gams cyclization ($POCl_3/CH_3CN$), most conveniently performed using the crude mixture of **8** and **9**, gave papaverine[12] (**10**) in 57% overall yield from **2a**.

For the preparation of C-1 unsubstituted isoquinolines, we capitalized on the facile hydrolysis[3] of 5-aryl-2-oxazo-

(2) For examples, see: Bills, J. L.; Naller, C. R. *J. Am. Chem. Soc.* **1948**, *70*, 957–62; Bruckner, V.; Foder, G.; Kiss, J.; Kovacs, J. *J. Chem. Soc.* **1948**, 885–90; also, ref 15.

(3) Schöllkopf, U.; Gerhart, F.; Hoppe, I.; Harms, R.; Hantke, K.; Scheunemann, K.-H.; Eilers, E.; Blume, E. *Justus Liebigs Ann. Chem.* **1976**, 183–202.

(4) Goszczynski, S.; Kopczynski, T. *J. Org. Chem.* **1973**, *38*, 1245–46. Fitton, A. O.; Frost, J. R.; Zakaria, M. M.; Andrew, G. *J. Chem. Soc., Chem. Commun.* **1973**, 889–90.

(5) Hoppe, D.; Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 301–02. Böll, W. A.; Gerhart, F.; Nurrenbach; Schöllkopf, U. *Ibid.* **1970**, *9*, 458–59.

(6) Barrett, A. G.; Barton, D. H. R.; Falck, J. R.; Papaioannou, D.; Widdowson, D. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 652–61. Falck, J. R. D.I.C. Thesis, Imperial College, London, 1974.

(7) Meyers, A. I.; Collington, E. W. *J. Am. Chem. Soc.* **1970**, *92*, 6676–78.

(8) Benzaldehydes react with 2-lithio-2-oxazolines to afford 2-substituted oxazolines. For a provocative application of lithiated oxazoles and oxazolines to alkaloid synthesis, see: Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1980**, *45*, 2548–50.

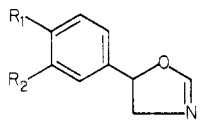
(9) For a review of substitution reactions using cuprates, see: Posner, G. H. *Org. React.* **1975**, *22*, 253–400.

(10) 2,2′-Bisoxazolines are useful precursors for *N,N′*-dihydroxyethylenediamines. Butula, I.; Karlovic, G. *Justus Liebigs Ann. Chem.* **1976**, 1455–64.

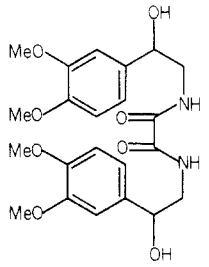
(11) Golding, B. T.; Hall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1302–08.

(12) For alternative papaverine synthesis see ref 8.

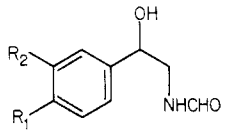
lines to *N*-(2-hydroxy-2-phenethyl)formamides. Thus, treatment of oxazolines **3a,b** and **11b** with dilute acetic acid in wet tetrahydrofuran (4 h) followed by extractive isolation afforded **12a–c**, respectively, in 85–93% yield. Bisoxazoline **3a** was similarly transformed to **13**. As expected, **12a,b** were smoothly cyclized to isoquinoline **14a,b** with $POCl_3$ in refluxing CH_3CN. Under identical conditions, **13** gave a complex product mixture.



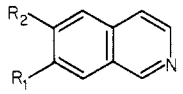
11



13



12



14

a, $R_1 = R_2 = OMe$; b, $R_1 = OMe$, $R_2 = OCH_2Ph$; c, $R_1 = R_2 = H$

Experimental Section

General Procedures. ^1H NMR spectra were obtained at 90 MHz on a JEOL FX-90Q spectrometer in $CDCl_3$, using tetramethylsilane as internal standard. Mass spectra were obtained with a Finnigan 4000 GC-MS. Infrared spectra were recorded on a Beckman Acculab 8. Melting-point determinations were performed with an Electrothermal melting-point apparatus in open capillaries and are uncorrected. Microanalyses were obtained from Galbraith Laboratories, Inc., Knoxville, TN. Anhydrous tetrahydrofuran and benzene were obtained by distillation from benzophenone ketyl under nitrogen; dry methylene chloride was distilled from P_2O_5.

Bisoxazoline 3a. To a stirred solution of **2a** (200 mg, 0.966 mmol) in 5 mL of dry THF at −78 °C was added dropwise *n*-BuLi (1.1 equiv, 0.975 mmol). After 75 min, the yellow, homogeneous solution was transferred via cannula to a stirred slurry of cuprous iodide (0.531 mmol) in 3 mL of THF at −78 °C. The heterogeneous mixture was kept at 4 °C overnight and then quenched with 0.5 mL of MeOH at −20 °C. The mixture was poured into ice–water and extracted with ether. The combined ethereal extracts were washed with water and brine, dried over Na_2SO_4, and evaporated. Fractional crystallization from CH_2Cl_2/Et_2O gave 62 mg of the less polar bisoxazoline isomer [TLC (5% MeOH/CH_2Cl_2) R_f ~0.47] as white crystals: mp 196 °C; NMR δ 3.86 (s, 12 H), 4.42–4.46 (m, 4 H), 5.63 (t, J = 8 Hz, 2 H), 6.85 (br s, 6 H); IR ($CHCl_3$) 1625, 1600, 1520, 1265, 1125, 1030 cm^{-1}; mass spectrum, m/e (relative intensity) 412 (M^+, 20), 205 (20), 179 (25), 164 (100). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.90; H, 5.92; N, 6.74.

Further crystallization of the above mother liquor yielded 21 mg of the more polar isomer (R_f ~0.44): mp 145–47 °C; NMR δ 3.82 (s, 12 H), 4.10 (dd, J = 8, 14 Hz, 2 H), 4.43 (dd, J = 8, 14 Hz, 2 H), 5.60 (t, J = 8 Hz, 2 H), 6.83 (br s, 6 H); IR ($CHCl_3$) 1625, 1600, 1520, 1470, 1270, 1130, 1030 cm^{-1}. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 63.93; H, 6.00; N, 6.69.

Bisoxazoline 3b. 5-Phenyl-2-oxazoline[3] **2b** (273 mg) was treated with *n*-BuLi (1.1 equiv) and cuprous iodide (194 mg) in the same manner described for the preparation of **3a**. Recrystallization (CH_2Cl_2/Et_2O) afforded 40 mg of the less polar isomer [TLC (10% MeOH/CH_2Cl_2) R_f ~0.74] as white needles: mp 180 °C; NMR δ 4.00 (dd, J = 8, 14 Hz, 2 H), 4.50 (dd, J = 8, 14 Hz, 2 H), 5.70 (t, J = 8 Hz, 2 H), 7.32 (s, 10 H); IR ($CHCl_3$) 1630, 1130 cm^{-1}; mass spectrum, m/e (relative intensity) 292 (M^+, 16), 251 (20), 249 (27), 146 (23), 128 (42), 104 (80), 44 (100). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 74.04; H, 5.39; N, 9.64.

Flash chromatography of the above mother liquor (SiO_2, 5% MeOH/CH_2Cl_2) gave 17 mg of the more polar isomer (R_f ~0.60) as a colorless oil: NMR δ 4.00 (dd, J = 8, 14 Hz, 2 H), 4.45 (dd, J = 10, 14 Hz, 2 H), 5.70 (t, J = 8 Hz, 2 H), 7.30 (s, 10 H); IR ($CHCl_3$) 1630, 1130 cm^{-1}; mass spectrum, m/e (relative intensity) 292 (M^+, 28), 146 (54), 128 (63), 104 (100).

5-(3,4-Dimethoxyphenyl)-2-oxazoline (2a). *n*-BuLi (74.5 mmol) was added dropwise over 20 min to a −78 °C solution of methyl isocyanide[6] (75 mmol) in 200 mL of anhydrous THF. After 40 min, veratraldehyde (73.5 mmol) in 120 mL of THF was added slowly to the yellow suspension of α-lithiomethyl isocyanide at such a rate that the temperature did not exceed −60 °C. Stirring was continued for 30 min, then 2 mL of MeOH was added, and the whole was allowed to warm to room temperature. Extractive isolation and crystallization (Et_2O) yielded 13.0 g of **2a** (85%): mp 49–50 °C; NMR δ 3.40–4.35 (complex m, 2 H), 3.88 (s, 6 H), 5.38 (dd, J = 8, 9 Hz, 1 H), 6.75–6.85 (m, 3 H), 6.94 (t, J = 3 Hz, 1 H); IR ($CHCl_3$) 1630 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.86; H, 6.30; N, 6.91.

Preparation[11] of 8 and 9. (3,4-Dimethoxyphenyl)acetyl chloride (414 mg, 1.93 mmol) in 18 mL of dry CH_2Cl_2 was added dropwise to a solution of **2a** (400 mg, 1 equiv) in 20 mL of dry CH_2Cl_2. After 30 min, water (35 mg, 1 equiv) and triethylamine (195 mg, 1 equiv) in 1.5 mL of dry THF were added slowly. The hydrolysis products were extracted after 30 min, washed with brine, and evaporated. NMR analysis showed a 2.2:1 mixture of **8** and **9**. An analytical sample of **8** was isolated by chromatography: mp 166–167 °C (EtOAc/Et_2O); NMR δ 3.44 (s, 2 H), 3.62 (m, 2 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 5.82 (m, 1 H), 6.61–6.84 (m, 3 H), 8.02 (s, 1 H); IR ($CHCl_3$) 3430, 1730, 1670, 1600 cm^{-1}; mass spectrum, m/e (relative intensity) 403 (M^+, 6), 338 (8), 279 (25), 208 (40). Anal. Calcd for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.64; H, 6.12; N, 3.62.

Formate **8** could be hydrolyzed with $NaHCO_3$ in aqueous THF for 3 h to give **9**, mp 126 °C (lit.[13] mp 127 °C).

Papaverine (10). $POCl_3$ (580 mg) was added dropwise to a refluxing solution of the above crude product of **8** and **9** in CH_3CN. After 1 h, the mixture was cooled, poured into ice–water, washed with Et_2O, basified with 2 N NH_4OH, and extracted with EtOAc. Chromatography gave 371 mg of papaverine (**10**, 57% from **2a**), identical with an authentic sample by NMR, TLC, and mixture melting point of the hydrochloride salts.

***N*-[2-Hydroxy-2-(3,4-dimethoxyphenyl)ethyl]formamide (12a).** Oxazoline **2a** (207 mg) was dissolved in 4 mL of THF and 1.5 mL of H_2O containing acetic acid (15 mg) and maintained until TLC analysis showed complete conversion (4 h). The solvent was evaporated and the residue extractively isolated to yield after crystallization 208 mg of **12a** (93%): mp 115 °C; NMR δ 3.04–3.85 (m, 2 H), 3.82 (s, 6 H), 4.75 (dd, J = 8 Hz, 1 H), 6.05–6.22 (br s, 1 H), 6.74–7.00 (m, 3 H), 8.12 (s, 1 H); IR ($CHCl_3$) 3600, 3400, 1695, 1610, 1600 cm^{-1}; mass spectrum, m/e (relative intensity) 225 (M^+, 9), 180 (18), 167 (72), 140 (44), 124 (18). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.58; H, 6.77; N, 6.38.

***N*-[2-Hydroxy-2-(3-benzyloxy-4-methoxyphenyl)ethyl]formamide (12b).** By the method described for the preparation of **12a**, oxazoline[6] **11b** was hydrolyzed to **12b** (88%): mp 99–101 °C (EtOAc); NMR δ 3.06–3.86 (m, 2 H), 3.83 (s, 3 H), 4.77 (dd, J = 8 Hz, 1 H), 5.08 (s, 2 H), 6.70–7.05 (m, 3 H), 7.29 (s, 5 H), 8.08 (s, 1 H); IR ($CHCl_3$) 3450, 1695, 1610, 1600 cm^{-1}; mass spectrum, m/e (relative intensity) 301 (M^+, 4), 283 (3), 255 (8), 242 (15), 91 (100). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.52; N, 4.74.

***N*-(2-Hydroxy-2-phenethyl)formamide (12c).** Following the procedure used to prepare **12a**, oxazoline **2b** was hydrolyzed to **12c** (85%) as a colorless oil whose spectral properties were consistent with literature values.[3]

Preparation of 13. By the method used to prepare **12a**, 40 mg of **3a** (less polar isomer) was hydrolyzed to give 39 mg of **13** (89%): mp 175 °C (CH_2Cl_2/Et_2O); NMR δ 3.22–3.64 (m, 4 H),

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3.82 (s, 6 H), 3.84 (s, 6 H), 4.75 (dd, J = 8 Hz, 2 H), 6.82–7.04 (m, 6 H); IR (KBr) 3400, 1650, 1510 cm^{-1}; mass spectrum, m/e (relative intensity) 448 (M^+, 4), 430 (23), 412 (22), 264 (13), 164 (100); high-resolution mass spectrum, calcd for $C_{22}H_{28}O_8N_2$ m/e 448.4718, found m/e 448.4668.

6,7-Dimethoxyisoquinoline (14a). To a refluxing solution of **12a** (1 g) in 40 mL of CH_3CN was added dropwise $POCl_3$ (2 mL) in 5 mL of CH_3CN. After 1 h, the mixture was cooled, the solvent evaporated, and the residue added to ice–water and then washed with ether. The aqueous layer was basified with concentrated NH_4OH and extracted with CH_2Cl_2. Chromatography furnished 0.628 g of **14a** (71%), mp 89–90 °C (lit.[14] mp 90–91 °C).

6-(Benzyloxy)-7-methoxyisoquinoline (14b). Following the procedure used to prepare **14a**, formamide **12b** was cyclized to **14b** (75%), mp 125–127 °C (lit.[15] mp 127–128 °C).

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Registry No. 2a, 78004-17-8; **2b**, 21857-14-7; **3a** (isomer 1), 78004-18-9; **3a** (isomer 2), 78004-19-0; **3b** (isomer 1), 78004-20-3; **3b** (isomer 2), 78004-21-4; **7**, 78004-22-5; **8**, 78004-23-6; **9**, 78004-24-7; **10**, 58-74-2; **11b**, 71146-40-2; **12a**, 78004-25-8; **12b**, 78004-26-9; **12c**, 58644-57-8; **13**, 78004-27-0; **14a**, 15248-39-2; **14b**, 78004-28-1; methyl isocyanide, 593-75-9; veratraldehyde, 120-14-9; (3,4-dimethoxyphenyl)acetyl chloride, 10313-60-7.

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Reduction of *gem*-Dibromides with Diethyl Phosphite

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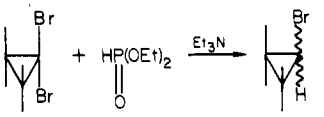
Much attention has been paid to the conversion of *gem*-dihalocyclopropanes to monohalocyclopropanes.[1] In most of dehalogenation reactions, however, reagents are limited to metallic ones such as organotin hydride,[1a] lithium aluminum hydride,[1b] sodium borohydride,[1c] Grignard reagent,[1d] and zinc–copper couple,[1e] and these methods have several disadvantages. Herein, we report a versatile reduction of *gem*-dibromo derivatives by using diethyl phosphite and triethylamine.

gem-Dibromocyclopropanes were treated with diethyl phosphite in the presence of triethylamine to give monobromocyclopropanes in good yields with the deposition of $Et_3N{\cdot}HBr$. Under the present reaction conditions, a further reduction of the resultant monobromide was not observed.



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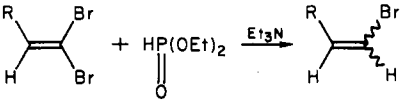
A variety of *gem*-dibromocyclopropanes were successfully reduced to the corresponding monobromides as shown in Table I. The dibromides, **1d** and **1e**, having an electron-withdrawing group were subject to the smooth debromination even at room temperature to produce the corresponding monobromocyclopropanes in 88% and 86% yields, respectively, without a chemical change of functional groups. This method could not be applied to the reduction of 7,7-dichloronorcarane (**1h**) under the same reaction conditions.

The absence of triethylamine apparently reduced the reduction yield, so triethylamine would play a significant part in the reaction. It was reported that dialkyl phosphite reacts with carbon tetrachloride in the presence of triethylamine to give dialkyl chlorophosphite and chloroform, in which the intermediate $(RO)_2PO^-$ was supported.[2] The same intermediate may be assumed in the present reaction path.

Dibromomalonamide has been reported to be reduced to malonamide with trialkyl phosphite in alcohol at room temperature.[3] By this method, however, 7,7-dibromonorcarane (**1f**) was not reduced, while the reduction of **1f** with diethyl phosphite and triethylamine occurred even at room temperature to produce the corresponding monobromide in 59% yield.

The present reduction method could be extended to the conversion of *gem*-dibromoalkenes into monobromoalkenes. β,β-Dibromostyrene (**2i**) reacted with 2 equiv of diethyl phosphite and triethylamine at room temperature for 4 h to give β-bromostyrene in 96% yield (trans/cis = 94:6). Similarly, the reduction of 1,1-dibromo-3-



methyl-4-phenyl-1,3-butadiene (**2k**) was performed to produce the corresponding monobromo diene, as shown in Table I. Since the dibromoalkenes are easily prepared from the aldehyde,[4] the present method is estimated as a convenient procedure for the preparation of 1-bromo-1-alkenes.

A similar reduction is expected in the reaction of *gem*-dibromoalkenes with trichlorosilane and triethylamine,[5] but the reaction of **2i** with 2 equiv of trichlorosilane and triethylamine at room temperature for 4 h gave β-bromostyrene in only 37% yield (trans/cis = 91:9).

Experimental Section

gem-Dibromocyclopropanes[6] and *gem*-dibromoalkenes[4] were prepared according to the reported procedures. Diethyl phosphite,

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