and melting points are summarized in Table I.

**5a** (R = 2-pyridyl): mp 132–134 °C (ether); mass spectrum, *m/e* 473 ($M^+$). Anal. Calcd $C_{26}H_{27}N_5O_4$ (473.536): C, 65.95; H, 5.75; N, 14.79. Found: C, 65.63; H, 5.94; N, 14.89. $\lambda_{max}$ 380 (infl.), 330 (infl.), 289 (log $\epsilon$ 4.59), 249 nm (4.33); $\nu_{max}$ 3270 (NH), 1710, 1700 (C=O)8 1640 $cm^{-1}$ (C=C).

**5b** (R = 3-pyridyl): mp 102–104 °C (ether); mass spectrum, *m/e* 473 ($M^+$). Anal. Calcd $C_{26}H_{27}N_5O_4$ (473.536): C, 65.95; H, 5.75; N, 14.79. Found: C, 66.12; H, 5.98; N, 14.62. $\lambda_{max}$ 382 (log $\epsilon$ 4.07), 326 (4.14), 278 (4.47), 250 nm (infl.); $\nu_{max}$ 3250 (NH), 1700 (C=O), 1655 $cm^{-1}$ (C=C).

**5c** (R = 4-pyridyl): mp 169–170 °C; mass spectrum, *m/e* 473 ($M^+$). Anal. Calcd $C_{26}H_{27}N_5O_4$ (473.536): C, 65.95; H, 5.75; N, 14.79. Found: C, 66.06; H, 5.68; N, 14.90. $\lambda_{max}$ 380 (infl.) 326 (log $\epsilon$ 4.04), 266 nm (4.36); $\nu_{max}$ 3260 (NH), 1700 (C=O), 1645 $cm^{-1}$ (C=C).

**Preparation of Ethyl 1,6-Dimethyl-2-oxo-3-(3,6-dipyridyl-4-pyridazinyl)-1,2-dihydropyridine-5-carboxylates 6a–c.** (a) **5a–c** (0.473 g, 1 mmol) were dissolved in 5–10 mL of ethanol. Water (5–10 mL) was added to the yellow solution, and the mixture was stirred at 25 °C for 5–6 h. The yellow color disappeared and white crystals separated, 2-Oxo-1,2-dihydropyridines **6a–c** were filtered off and washed with water.

**6a** (R = 2-pyridyl): yield, 0.376 g (88%); mp 210–211 °C (EtOH); mass spectrum, *m/e* 427 ($M^+$). Anal. Calcd $C_{24}H_{21}N_5O_3$ (427.465): C, 67.44; H, 4.95; N, 16.38. Found: C, 67.19; H, 5.06; N, 16.19. $\lambda_{max}$ 330 (infl.), 280 (log $\epsilon$ 4.58), 250 nm (infl.); $\nu_{max}$ 1710 (C=O, ester), 1660 $cm^{-1}$ (C=O, ring).

**6b** (R = 3-pyridyl): yield, 0.316 g (74%); mp 204–205 °C (EtOH); mass spectrum, *m/e* 427 ($M^+$). Anal. Calcd $C_{24}H_{21}N_5O_3$ (427.465): C, 67.44; H, 4.95; N, 16.38. Found: C, 67.11; H, 5.13; N, 16.28. $\lambda_{max}$ 332 (log $\epsilon$ 3.99), 270 nm (4.50); $\nu_{max}$ 1708 (C=O, ester), 1665 $cm^{-1}$ (infl. C=O, ring).

**6c** (R = 4-pyridyl): yield, 0.324 g (76%); mp 240–241 °C (EtOH); mass spectrum, *m/e* 427 ($M^+$). Anal. Calcd $C_{24}H_{21}N_5O_3$ (427.465): C, 67.44; H, 4.95; N, 16.38. Found: C, 67.25; H, 5.16; N, 16.31. $\lambda_{max}$ 336 (log $\epsilon$ 3.94), 262 (4.53), 236 nm (infl.); $\nu_{max}$ 1710 (C=O, ester), 1659 $cm^{-1}$ (C=O, ring).

(b) A mixture of **1d** (1.069 g, 4 mmol), **2a–c** (1.889 g, 8 mmol), and 100 mL of 96% EtOH was stirred at reflux temperature for 4 h. The solvent was removed with a rotary evaporator, then $CHCl_3$ (10 mL) was added, and the insoluble 1,2-dihydrotetrazine **4a–c** was filtered off. The filtrate was evaporated to dryness, the residue was recrystallized from EtOH to give 2-oxo-1,2-dihydropyridines **6a–c** in 56%, 78%, and 64% yields: mp 210–211, 204–206, and 240–241 °C, respectively.

**Preparation of Diethyl 4-(Methylamino)-1-[3,6-di-2-pyridyl-4-pyridazinyl]-1,3-pentadiene-1,3-dicarboxylate (5a) from Diethyl 1,6-Dimethyl-2-methylene-1,2-dihydropyridine-3,5-dicarboxylate (7). 3a** (2.51 g, 10 mmol) and 1.75 mL of dimethyl sulfate were stirred at 60 °C for 6 h. 1,2,6-Trimethylpyridinium methylsulfate was extracted with ether (4 × 15 mL) to remove the excess of dimethyl sulfate and then was dissolved in water (10 mL). $Na_2CO_3$ (3.39 g, 32 mmol) was added, and the mixture was stirred at 25 °C for 5 min, extracted with $CHCl_3$ (3 × 30 mL), dried over $MgSO_4$, and evaporated to dryness. 2-Methylene compound **7** was isolated as red oil (2.62 g, 98.1%). **7** and tetrazine **2a** (2.24 g, 9,5 mmol) were dissolved in toluene (100 mL) and were refluxed for 45 min. Toluene was removed by a rotary evaporator, and the residue was purified by column chromatography using ethyl acetate as eluent. **5a** (2.60 g, 56%) was isolated as yellow solid: mp 134–135 °C (from ether).

**Crystallography. Crystal data for 5a**: $C_{26}H_{27}N_5O_4$, for = 473.54; triclinic; $a$ = 10.655 (1) Å, $b$ = 11.042 (1) Å, $c$ = 11.751 (3) Å; $\alpha$ = 64.02 (2)°, $\beta$ = 83.57 (2)°, $\gamma$ = 81.02 (2)°; $D_{calcd}$ = 1.202 g $cm^{-3}$; $Z$ = 2; crystal size 0.3 × 0.4 × 0.5 mm; space group $P\bar{1}$; $\lambda$(Cu K$\bar{\alpha}$ = 1.5418 Å). Data were collected on an automated four-circled Enraf-Nonius CAD-4 diffractometer with monochromated Cu K$\bar{\alpha}$ radiation ($\theta_{range}$ 1.5–75.0°): $N_{tot}$ 5046; $N_R$ 4304 [$I > 3\sigma(I)$]; $N_{par}$ 317 + 108. The initial structure model was developed by direct method[24] (MULTAN 83) applied for 450 $E$ values and included all 35 non-H atoms. After anisotropic full-matrix refinement for the non-hydrogen atoms the hydrogen atoms were obtained from difference electron-density (e.d.) synthesis, and their parameters were refined isotropically before the final anisotropic refinement for the non-hydrogen atoms ($R_R$ = 0.054, $R_w$ = 0.088). The final $\Delta F$ map contained features ranging from 0.25 to 0.30 e/Å$^3$.

**Crystal data for 6b**: $C_{24}H_{21}N_5O_3$, fw = 427.47; monoclinic; $a$ = 18.497 (1) Å, $b$ = 5.880 (2) Å, $c$ = 19.228 (2) Å; $\beta$ = 104.82 (2)°; $D_{calcd}$ = 1.404 g $cm^{-3}$; $Z$ = 4; crystal size 0.1 × 0.1 × 0.4 mm; space group $P2_1/c$; $\lambda$(Cu K$\bar{\alpha}$ = 1.5418 Å). Data were collected and processed much the same way as for **5a**, including structure solution and refinement: $\theta_{range}$ 1.5–75.0°; $N_{tot}$ 4171; $N_R$ 2296 [$I > 3\sigma(I)$]; $N_{par}$ 290 + 84; $R_R$ = 0.040; $R_w$ = 0.039. The final $\Delta F$ map contained peaks ranging from 0.20 to 0.26 e/Å$^3$.

**Acknowledgment.** We are indepted to Dr. Y. Houbrechts for 300-MHz NMR spectra. We thank T. Erös-Takàcsy for the mass spectral data. The sample of K-10 montmorillonite was kindly supplied by Süd-Chemie, Munich. We are grateful to Dr. A. Mathy for helpful suggestions. One of us (M.B.) was the recipient of a post-doctoral fellowship from Communauté Francaise de Belgique. We have also benefited from support of Fonds National de la Recherche Scientifique, Brussels, and of Programmation de la Politique Scientifique (Action Concertée 82/87-34).

**Supplementary Material Available:** Characteristics of the redox reactions 1 + 2, $^{13}C$ NMR chemical shifts for compounds **5a–c** and **6a–c**, and bond lengths, bond angles, torsion angles, and relative atomic coordinates for **5a** and **6b** (9 pages). Ordering information is given on any current masthead page.

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# Total Synthesis of (±)-5-*O*-Methyllicoricidin

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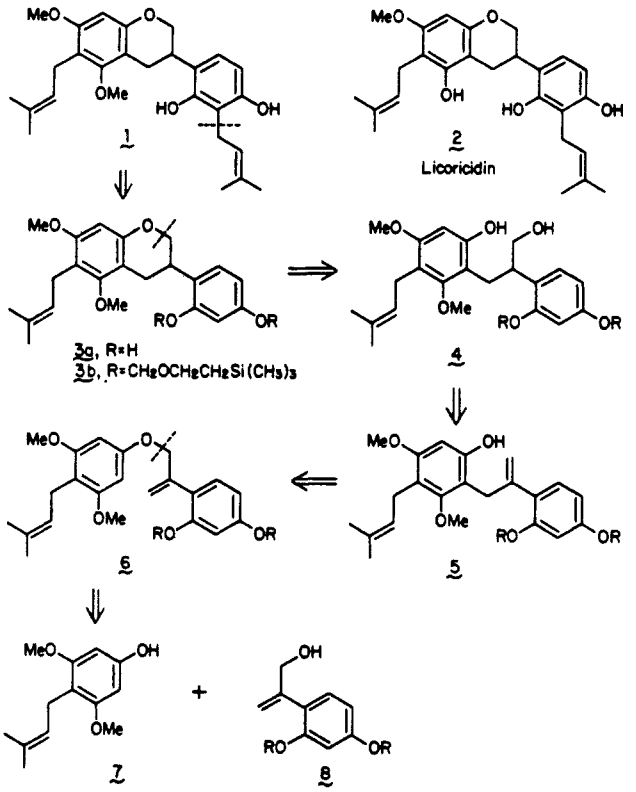
*Received December 1, 1986*

A novel intramolecular Mitsunobu alkylation is employed to construct the benzopyran moiety of the newly isolated isoflavan 5-*O*-methyllicoricidin. This convergent 15-step total synthesis outlines a chemically mild approach to the acid-sensitive isoflavanoids.

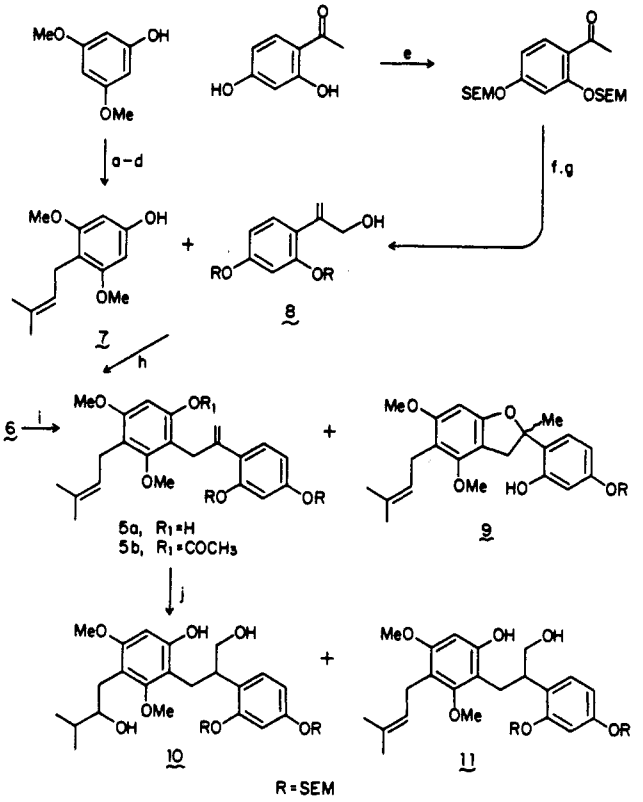
For centuries the dried rhizomes and roots of the genus *Glycyrrhiza* (Leguminosae) have been used in both Asia and Europe as a herbal remedy for respiratory and peptic ailments. A principal isoflavandiol ingredient was isolated

0022-3263/87/1952-2029$01.50/0 

**Scheme I**




**Scheme II**[a]




[a] Key: (a) *tert*-butyldimethylsilyl chloride, triethylamine; (b) *n*-butyllithium, ether; (c) prenyl bromide; (d) tetra-*n*-butylammonium fluoride; (e) SEM-chloride, triethylamine; (f) methylenetriphenylphosphorane, THF; (g) selenium dioxide and *tert*-butyl hydroperoxide; then sodium borohydride; (h) triphenylphosphine–diethyl azodicarboxylate; (i) acetic anhydride, sodium acetate, 210 °C, ; (j) borane or 9-BBN.

and characterized[1] from the Chinese herb *Glycyrrhiza uralensis Fisch.* The structure of this compound **1** was initially deduced from NMR, IR, and mass spectral data. It is a methyl analogue of a known isoflavan, licoricidin (**2**), first isolated in 1968 from *Glycyrrhiza glabra sp.*[2] and recently from *G. uralensis.*[3] We report that the structure of **1** has been confirmed by total synthesis.

The retrosynthetic strategy used is depicted in Scheme I. Although isoflavans are ubiquitous structures in plant natural products, their laboratory syntheses have been limited to relatively robust moieties that can survive the classical acid-catalyzed cyclizations, hydrogenolysis of benzylic hydroxyls, and reduction of oxonium intermediates.[4] In this particular problem, the presence of the sensitive prenyl units demands a more subtle approach. Retrosynthetically, the prenyl unit ortho to the free phenolic groups was projected to be introduced via a nuclear alkylation of precursor **3a**. Disconnection at the benzopyran ring of **3a** produced a phenolic alcohol synthon **4**, which was deemed amenable to cyclization via a variety of methods. This phenolic intermediate was to be obtained via the coupling of subunits **7** and **8**, followed by a Claisen rearrangement to **5** and a selective hydroboration at the less substituted olefin.[5]

## Results and Discussion

The two subunits **7** and **8** were prepared readily as shown in Scheme II. Thus, commercially available 3,5-dimethoxyphenol was silylated, metalated, alkylated, and desilylated to afford **7** in 59% overall yield. Subunit **8** was obtained by blocking the phenolic functions of commercially available 2,4-dihydroxyacetophenone with [β-(trimethylsilyl)ethoxy]methyl chloride (SEM-chloride[6]) and Wittig olefination followed by selenium dioxide allylic oxidation. The coupling of these two subunits was accomplished smoothly through the application of the Mitsunobu reaction.[7] The product **6** (R = SEM) appears to be sensitive on prolonged exposure to silica gel but will tolerate a rapid flash chromatographic separation[8] from the other reaction byproducts. When **6** was subjected to a Claisen rearrangement in *N,N*-dimethylaniline at 210 °C, the expected product **5a** and an unexpected benzofuran derivative **9** were produced in a 4:1 ratio (30% yield). Substitution of acetic anhydride and sodium acetate for the dimethylaniline in this reaction produced **5b** in 49% yield with no trace of **9**. In addition, the rate and degree of conversion were enhanced in the acetic anhydride system. Products **5a** and **5b** are also sensitive to silica gel, since attempts to purify them resulted in decreased yields

(1) We thank Dr. T. Lam for communicating his structural assignment to us and for providing an authentic sample of **1** for comparison with the synthetic product. U.S. Patent Application Serial No. 656 554, manuscript in preparation.

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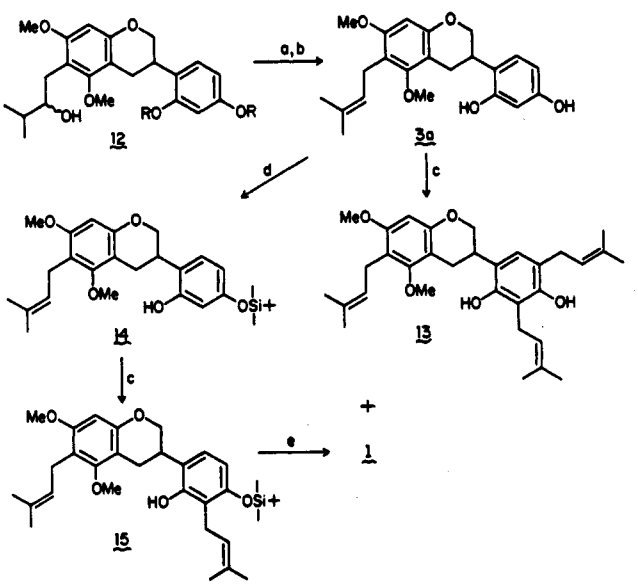
(7) Mitsunobu, O. *Synthesis* **1981**, 1.

(8) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

**Scheme III**[a]



[a] Key: (a) triphenylphosphine–diethyl azodicarboxylate; (b) methanol, sulfuric acid; (c) *n*-butyllithium, prenyl bromide; (d) triethylamine, *tert*-butyldimethylsilyl chloride; (e) pyridine–hydrogen fluoride, THF.

and the appearance of more polar products. With **5** in hand, we examined a variety of hydroborating agents with the goal of effecting a regiospecific hydroxylation at the styrene terminus to produce **11**. Despite the application of more selective hydroborating agents (9-borabicyclo-[3.3.1]nonane (9-BBN), disiamylborane), there appeared to be very little kinetic difference in the hydroboration of the prenyl unit and a phenyl-disubstituted olefin. One obtained, when reaction was observed, the bishydroborated product **10** as a racemic diastereomeric mixture.

Although it appears that our approach to intermediate **3b** could not be realized through **11**, we resorted to utilizing **10** as an alternative in order to test our cyclization strategy. Upon treatment with an 8-fold excess of 1:1 triphenylphosphine–diethyl azodicarboxylate (TPP–DEAD) complex in tetrahydrofuran (THF), **10** was rapidly cyclized to **12** (Scheme III), a benzopyran with a hydroxyl group in the latent prenyl side chain that slowly underwent a subsequent dehydration to afford **3b** in 83% overall yield. This unforeseen gratuitous dehydration proceeds with high regiospecificity. The regiospecificity of this dehydration leading to the unconjugated olefin may be rationalized by invoking unfavorable A-strain interaction in the transition state leading to the conjugated product.

With intermediate **3b** in hand, further elaboration to **3a** involved the removal of the SEM groups. In this case, the use of fluoride reagents was totally ineffective. However, the use of 1% methanolic sulfuric acid smoothly transformed **3b** to **3a** in 90% yield. The final task of introducing the prenyl group was not a trivial exercise. Treatment of **3a** with 2 equiv of *n*-butyllithium in toluene and prenyl bromide produced a complex mixture of which **1** was a minor component (5% isolated yield) in addition to **13** (the bisalkylated product in 30% yield). It appears that the initial C-alkylation of the diolate leads to **1**, which is further alkylated at a faster rate to **13**. This problem was circumvented by selectively blocking the least hindered hydroxyl function of **3a** with *tert*-butyldimethylsilyl chloride to afford **14**. Nuclear alkylation[9] using *n*-butyllithium and prenyl bromide in toluene produced **15** in 48% yield. Subsequent desilylation with HF–pyridine complex in THF afforded **1** (85%), which exhibited $^1$H NMR (200-MHz), mass spectral, and IR data identical with that of the natural product.

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## Experimental Section

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 137 spectrophotometer. $^1$H NMR spectra were obtained in deuteriochloroform on a Varian XL-200 spectrometer. All data are reported (ppm) relative to tetramethylsilane. Mass spectra were recorded on Varian Mat Bremen 731 and Mat 212 Finnigan spectrometers. Elemental analyses were determined by the Analytical Laboratory of MSDRL, Rahway, Merck & Co. Flash column chromatography was carried out on Merck silica gel 60, 230–400 mesh. Thin-layer chromatography (TLC) was performed on Analtech silica gel GF plates. All solvents (ether, tetrahydrofuran (THF), toluene) were distilled under nitrogen from sodium benzophenone ketyl before use. All starting materials were obtained from Aldrich Chemical Co. The resealable tube used in the Claisen rearrangement was cleaned, soaked in a concentrated ammonium hydroxide solution, and dried in an oven overnight before use.

**3,5-Dimethoxyphenol *tert*-Butyldimethylsilyl Ether (16).** To 5 g (32 mmol) of 3,5-dimethoxyphenol in 70 mL of dichloromethane were added 5.1 g (34 mmol) of *tert*-butyldimethylsilyl chloride, 100 mg of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), and 7 mL of triethylamine. After 5 h at 20 °C, the solvent was removed in vacuo, and the residue was flash chromatographed through 100 g of silica gel with dichloromethane as eluent. The product was collected in one fraction (3 column volumes). Evaporation of the solvent in vacuo afforded 8.7 g (99%) of pure product as a colorless oil: IR (film) 2941, 1613, 1471, 1256, 1211, 1198, 1160, 1064, 844 cm$^{-1}$; $^1$H NMR $\delta$ 0.20 (s, 6 H), 0.99 (s, 9 H), 3.75 (s, 6 H) 6.05 (d, 2 H, $J$ = 2 Hz), 6.15 (t, 1 H, $J$ = 2 Hz). The title compound was carried on to the subsequent experiment without further characterization.

**3,5-Dimethoxy-4-(3-methyl-2-butenyl)phenol *tert*-Butyldimethylsilyl Ether (17).** To 7 g (26 mmol) of **16** in 20 mL of diethyl ether under nitrogen was added via syringe 10.5 mL of a 2.7 M solution of *n*-butyllithium in hexane. The solution was stirred at 20 °C for 90 h and then treated with 3.0 mL (25.4 mmol) of prenyl bromide dropwise over 5 min. The mixture was stirred at 20 °C an additional 50 h. The reaction mixture was quenched with 50 mL of cold saturated aqueous ammonium chloride solution and extracted with ether. The ether extracts were combined and dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to afford 7.5 g of unpurified product. Flash chromatographic purification (300 g of silica gel, 5.5 × 40 cm column, 500 mL of hexane followed by 5% ethyl acetate–hexane, 25-mL fractions) afforded 5.2 g (60%) of pure product as a waxy solid: mp 60–62 °C; IR ($CCl_4$) 2915, 1587, 1486, 1453, 1445, 1406, 1217, 1163, 1151, 1119, 1019, 841 cm$^{-1}$; $^1$H NMR $\delta$ 0.20 (s, 6 H), 0.99 (s, 9 H), 1.66 (s, 3 H), 1.76 (s, 3 H), 3.26 (d, 2 H), 3.77 (s, 6 H), 5.18 (m, 1 H), 6.06 (s, 2 H); $R_f$(17) 0.61 (silica gel, 10% ethyl acetate–hexane). Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.69; H, 9.39.

**3,5-Dimethoxy-4-(3-methyl-2-butenyl)phenol (7).** To 5 g (15 mmol) of **17** in 15 mL of tetrahydrofuran (THF) under nitrogen was added 15 mL of a 1.0 M solution of tetra-*n*-butylammonium fluoride in THF. The reaction mixture was stirred for 3 h at 20 °C, and then the solvent was removed in vacuo. The residue was flash chromatographed (150 g of silica gel, 5.5 × 40 cm column, 2 column volumes of 20% ethyl acetate–hexane, 2 column volumes of ethyl acetate) to afford 3.29 g (99%) of pure product: IR (film) 3257, 2899, 1600, 1464, 1200, 1192, 1120, 997, 816, 797 cm$^{-1}$; $^1$H NMR $\delta$ 1.66 (s, 3 H), 1.76 (s, 3 H), 3.26 (d, 2 H, $J$ = 7 Hz), 3.78 (s, 6 H), 5.18 (m, 1 H), 6.08 (s, 2 H), 7.40 (s, 1 H); $R_f$(7) 0.08 (silica gel, 5% ethyl acetate–hexane). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.05; H, 8.33.

**2,4-Bis[[2-(trimethylsilyl)ethoxy]methoxy]acetophenone (19).** To 23.5 g (141.1 mmol) of SEM-chloride[6] in 50 mL of benzene were added 6.0 g (39.4 mmol) of 2,4-dihydroxyacetophenone, 80 mg DMAP, and 22 mL of triethylamine. At the end

of the triethylamine addition a tan slurry resulted. The heterogeneous mixture was then heated with an oil bath at 110 °C for 3 h. Ether was added to the cooled mixture to precipitate out triethylamine hydrochloride, and the mixture was filtered. The filtrate was concentrated in vacuo to a reddish oil. Flash chromatography (100 g of silica gel, 5.5 × 40 cm column, 4% MeOH–$CH_2Cl_2$) afforded 16 g (98%) of pure product as a clear oil: IR (neat) 2910, 2877, 1668, 1601, 1246, 1092, 1006, 860, 838 $cm^{-1}$; $^1H$ NMR $\delta$ 0.02 (s, 18 H), 1.0 (m, 4 H), 2.64 (s, 3 H), 3.81 (m, 4 H), 5.30 (s, 2 H), 5.36 (s, 2 H), 6.77 (dd, 1 H, $J$ = 3, 8 Hz), 6.90 (d, 1 H, $J$ = 3 Hz), 7.84 (d, 1 H, $J$ = 8 Hz). Anal. Calcd for $C_{20}H_{36}O_5Si_2$: C, 58.21; H, 8.79. Found: C, 58.07; H, 8.74.

**[[4-(1-Methylethenyl)-1,3-phenylene]bis[[(oxymethylene)oxy]-2,1-ethanediyl]]bis(trimethylsilane) (20).** To 2.0 g (4.9 mmol) of methyltriphenylphosphonium iodide in 30 mL of dry THF under nitrogen was added 2 mL of a 2.7 M hexane solution of *n*-butyllithium. The mixture was stirred at 20 °C for 1.5 h, and 2.0 g (4.9 mmol) of **19** was then added in one portion. The reaction was quenched after 45 min with 1 mL of methanol and stirred an additional 3 h at 20 °C. Hexane was added to precipitate the triphenylphosphine oxide, and the slurry was filtered through a plug of silica gel with ether as eluent. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (60 g of silica gel, 3.5 × 40 cm column, 5% ethyl acetate–hexane) to afford 1.5 g (75%) of product as a clear oil: IR (film) 2924, 2865, 1613, 1497, 1250, 1095, 1010, 862, 838 $cm^{-1}$; $^1H$ NMR $\delta$ 0.02 (s, 18 H), 0.98 (m, 4 H), 2.11 (s, 3 H), 3.79 (m, 4 H), 5.04 (br s, 1 H), 5.12 (br s, 1 H), 5.20 (s, 2 H), 5.22 (s, 2 H), 6.68 (dd, 1 H, $J$ = 3, 8 Hz), 6.86 (d, 1 H, $J$ = 3 Hz), 7.11 (d, 1 H, $J$ = 8 Hz). Anal. Calcd for $C_{21}H_{38}O_4Si_2$: C, 61.41; H, 9.33. Found: C, 61.07; H, 9.36.

**α-Methylene-2,4-bis[[2-(trimethylsilyl)ethoxy]methoxy]-benzeneethanol (8).** To 5 g (1.2 mmol) of olefin **20** in 25 mL of dichloromethane in a 1-L flask was added with stirring in order 10 mL of *tert*-butyl hydroperoxide, 110 mg of selenium dioxide,[10] and 100 mg of salicylic acid. The mixture was stirred at 20 °C for 16 h. Isopropyl alcohol (100 mL) was added, and the mixture was cooled to 0 °C. Sodium borohydride (9.5 g) was then added in portions at a rate that minimized foaming, followed by 4 mL of a 10% NaOH solution and 30 mL of water. After the mixture was stirred at 0 °C for 1 h, 150 mL of a saturated aqueous solution of ammonium chloride was added slowly with cooling. After an additional 2 h at 0 °C, the solution turned cloudy and a reddish precipitate was observed. The mixture was extracted with 3 × 200 mL portions of ethyl acetate. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil. Flash chromatographic purification (200 g silica gel, 5.5 × 40 cm column; 800 mL of 10% ethyl acetate–hexane forerun was collected, which contained impurities; 800 mL of 50% ethyl acetate–hexane was used to elute the product) afforded 4.34 g (84%) of pure product as a clear oil: IR (film) 3418, 2927, 2869, 1609, 1581, 1500, 1247, 1084, 1007, 864, 838 $cm^{-1}$; $^1H$ NMR $\delta$ 0.02 (s, 18 H), 0.98 (m, 4 H), 3.78 (m, 4 H), 4.46 (d, 2 H, $J$ = 6 Hz), 5.21 (s, 1 H), 5.23 (s, 2 H), 5.24 (s, 2 H), 5.40 (m, 1 H), 6.74 (dd, 1 H, $J$ = 2, 8 Hz), 6.88 (d, 1 H, $J$ = 2 Hz), 7.18 (d, 1 H, $J$ = 8 Hz); exact mass calcd for $C_{21}H_{38}O_5Si_2$ 426.2258, found 426.2259.

**[[4-[1-[[3,5-Dimethoxy-4-(3-methyl-2-butenyl)phenoxy]-methyl]ethenyl]-1,3-phenylene]bis[[(oxymethylene)oxy]-2,1-ethanediyl]]bis(trimethylsilane) (6).** To 1.06 g (4.8 mmol) of phenol **7** and 1.84 g (4.3 mmol) of allylic alcohol **8** in a 100-mL pear-shaped flask was added 5 mL of benzene. The flask was then evacuated to azeotrope moisture with the benzene at 20 °C. Argon was used to refill the system, and 6 mL of freshly distilled THF was added to the flask to form a clear solution. In a separate flask under argon were added 1.40 g (5.3 mmol) of triphenylphosphine, 10 mL of THF, and 1.1 g (6.3 mmol) of diethyl azodicarboxylate (DEAD). This solution of triphenylphosphine–DEAD complex was added immediately in one portion to the stirred solution of **7** and **8**. The mixture was stirred 2 h at 20 °C before 300 μL of DEAD was added to complex the excess triphenylphosphine. After 1 h, the THF was removed in vacuo, and the residue was introduced onto 100 g of silica gel and flash filtered with 350 mL of 10% ethyl acetate–hexane. Evaporation of the filtrate in vacuo afforded 1.3 g (50%) of **6**, which was carried on to the next step without further purification. Due to its sensitivity to silica gel, only a small sample was rechromatographed to provide an analytical sample: IR (film) 2962, 1604, 1493, 1241, 1191, 1162, 1145, 1114, 1010, 862, 840 $cm^{-1}$; $^1H$ NMR $\delta$ 0.01 (s, 9 H), 0.04 (s, 9 H), 0.99 (m, 4 H), 1.70 (s, 3 H), 1.80 (s, 3 H), 3.30 (d, 2 H, $J$ = 8 Hz), 3.80 (s, 6 H), 3.80 (m, 4 H), 4.88 (s, 2 H), 5.25 (br m, 1 H), 5.26 (s, 2 H), 5.27 (s, 2 H), 5.30 (d, 1 H, $J$ = 2 Hz), 5.53 (d, 1 H, $J$ = 2 Hz), 6.22 (s, 2 H), 6.76 (dd, 1 H, $J$ = 2, 8 Hz), 6.92 (d, 1 H, $J$ = 2 Hz), 7.22 (d, 1 H, $J$ = 8 Hz); $R_f$(**6**) 0.42 (silica gel, 10% ethyl acetate–hexane). Anal. Calcd for $C_{34}H_{54}O_7Si_2$: C, 64.72; H, 8.63. Found: C, 64.54; H, 8.53.

**2-[2-[2,4-Bis[[2-(trimethylsilyl)ethoxy]methoxy]-phenyl]-2-propenyl]-3,5-dimethoxy-4-(3-methyl-2-butenyl)-phenol Acetate (5b).** To 585 mg (0.93 mmol) of **6** and 700 mg (8.5 mmol) of anhydrous sodium acetate in a resealable tube under argon was added 19.5 mL of freshly distilled acetic anhydride. The tube was sealed, and the mixture was heated in a 210 °C oil bath for 1 h, cooled to 20 °C, and worked up by ethyl acetate extraction from ice–water. The organic extracts were combined, dried ($MgSO_4$), and evaporated in vacuo. The residue was flash chromatographed (75 g of silica gel, 300 mL of 5% EtOAc–hexane, 300 mL of 10% EtOAc–hexane, 300 mL of 30% EtOAc–hexane) to afford 290 mg (49%) of product as an oil: IR (film) 2910, 1765, 1604, 1207, 1112, 1070, 1012, 859, 838 $cm^{-1}$; $^1H$ NMR $\delta$ 0.01 (s, 9 H), 0.03 (s, 9 H), 1.0 (m, 4 H), 1.72 (s, 3 H), 1.82 (s, 3 H), 2.26 (s, 3 H), 3.39 (d, 2 H, $J$ = 7 Hz), 3.69 (s, 2 H), 3.76 (s, 3 H), 3.80 (m, 4 H), 3.84 (s, 3 H), 4.76 (br s, 1 H), 5.02 (br s, 1 H), 5.26 (m, 1 H), 5.26 (s, 2 H), 5.29 (s, 2 H), 6.50 (s, 1 H), 6.72 (dd, 1 H, $J$ = 2, 8 Hz), 6.92 (d, 1 H, $J$ = 2 Hz), 7.12 (d, 1 H, $J$ = 8 Hz); $R_f$(**5b**) 0.28 (silica gel, 10% EtOAc–hexane); exact mass calcd for $C_{36}H_{56}O_8Si_2$ 672.3514, found 672.3511.

**β-[2,4-Bis[[2-(trimethylsilyl)ethoxy]methoxy]phenyl]-6-hydroxy-3-(2-hydroxy-3-methylbutyl)-2,4-dimethoxybenzenepropanol (10).** To 250 mg (0.37 mmol) of **5b** under nitrogen was added 9.0 mL of a 0.5 M solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in THF. The mixture was stirred at 20 °C for 17 h. The reaction was then cooled to 0 °C and quenched with 5 mL of water, 14 mL of methanol, 2 mL of a 30% hydrogen peroxide solution, and 2 mL of a 10% sodium hydroxide solution. After the mixture was stirred at 20 °C for 1 h, water was added and the products were extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by flash chromatography (75 g of silica gel, 3.5 × 40 cm column, successive elution with 200 mL of 10, 20, 30, and 40% EtOAc–hexane) to afford 186 mg (75%) of a racemic mixture of diastereomers: IR (film) 3283, 2910, 1606, 1500, 1244, 1076, 1014, 862, 837, 791 $cm^{-1}$; $^1H$ NMR $\delta$ 0.01 (s, 9 H), 0.03 (s, 9 H), 0.99 (m), 1.7 (m, 1 H), 2.5–3.2 (m, 5 H), 3.58 (br s, 2 H), 3.71 (s, 3 H), 3.75 (m), 3.82 (s, 3 H), 5.24 (s, 2 H), 5.30 (m, 2 H), 6.42 (s, 1 H), 6.78 (dd, 1 H, $J$ = 2, 8 Hz), 6.95 (d, 1 H, $J$ = 2 Hz), 7.44 (dd, 1 H, $J$ = 8, 8 Hz); $R_f$(**10**) 0.32 (silica gel, 2:1 hexane–EtOAc); exact mass calcd for $C_{34}H_{58}O_9Si_2$ 666.3619, found 666.3616.

**[[4-[3,4-Dihydro-5,7-dimethoxy-6-(3-methyl-2-butenyl)-2*H*-1-benzopyran-3-yl]-1,3-phenylene]bis[[(oxymethylene)oxy]-2,1-ethanediyl]]bis(trimethylsilane) (3b).** To 268 mg (0.4 mmol) of **10** in 8 mL of THF under nitrogen was added in one portion a solution of 1 g (3.8 mmol) of triphenylphosphine and 600 μL of DEAD in 6 mL of THF. Analysis (silica gel, 10% EtOAc–hexane) of the reaction mixture after 1 h indicated the presence of **3b** ($R_f$ 0.43) and **12** ($R_f$ 0.32). After 22 h at 20 °C, TLC indicated the complete conversion of **12** to **3b**. To the mixture was then added 150 μL of DEAD to complex the excess triphenylphosphine, and the THF was removed in vacuo at 20 °C. The residue was dissolved in 2 mL of $CH_2Cl_2$ and flash chromatographed (50 g of silica gel, 3.5 × 40 cm column, 200 mL of 10% EtOAc–hexane) to afford 210 mg (83%) of **3b** as an oil: IR (film) 2902, 1609, 1586, 1246, 1200, 1128, 1097, 1012, 859, 838 $cm^{-1}$; $^1H$ NMR $\delta$ 0.01 (s, 9 H), 0.03 (s, 9 H), 1.0 (m, 4 H), 1.72 (s, 3 H), 1.82 (s, 3 H), 2.84 (dd, 1 H, $J$ = 11, 16 Hz), 3.06 (dd, 1 H, $J$ = 6, 16 Hz), 3.34 (d, 2 H, $J$ = 7 Hz), 3.58 (br m, 1 H), 3.76 (s, 3 H), 3.79 (m, 4 H), 3.82 (s, 3 H), 4.06 (t, 1 H, $J$ = 11 Hz), 4.34 (d, 1 H, $J$ = 11 Hz), 5.25 (m, 1 H), 5.25 (s, 2 H), 5.29 (s, 2 H), 6.31 (s, 1 H), 6.75 (dd, 1 H, $J$ = 3, 9 Hz), 6.96 (d, 1 H, $J$ = 3 Hz), 7.10

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(d, 1 H, $J$ = 9 Hz); exact mass calcd for $C_{34}H_{54}O_7Si_2$ 630.3408, found 630.3405.

**4-[3,4-Dihydro-5,7-dimethoxy-6-(3-methyl-2-butenyl)-2*H*-1-benzopyran-3-yl]-1,3-benzenediol (3a).** To 210 mg (0.33 mmol) of **3b** in 10 mL of methanol and 10 mL of THF was added a solution of 0.3 mL of concentrated sulfuric acid in 10 mL of methanol. The mixture was stirred at 20 °C for 2 h and then neutralized with a cold solution of sodium bicarbonate. The mixture was extracted with ethyl acetate, and the combined extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. The product was purified by preparative TLC (2:1 hexane–EtOAc) to afford 112 mg (90%) of **3a** as an oil: IR (film) 3305, 2910, 1614, 1200, 1119 cm$^{-1}$; $^1$H NMR $\delta$ 1.68 (s, 3 H), 1.78 (s, 3 H), 2.87 (dd, 1 H, $J$ = 11, 16 Hz), 3.03 (ddd, 1 H, $J$ = 2, 6, 16 Hz), 3.31 (d, 2 H, $J$ = 6 Hz), 3.45 (m, 1 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 4.06 (t, 1 H, $J$ = 11 Hz), 4.32 (complex d, 1 H), 5.08 (br s, 1 H), 5.21 (t, 1 H, $J$ = 6 Hz), 5.30 (s, 1 H), 6.28 (s, 1 H), 6.30 (d, 1 H, $J$ = 3 Hz), 6.39 (dd, 1 H, $J$ = 3, 8 Hz), 6.98 (d, 1 H, $J$ = 8 Hz); $R_f$(**3a**) 0.27 (silica gel, 2:1 hexane–EtOAc); exact mass calcd for $C_{22}C_{28}O_5$ 370.1780, found 370.1779.

**2-[3,4-Dihydro-5,7-dimethoxy-6-(3-methyl-2-butenyl)-2*H*-1-benzopyran-3-yl]-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenol (14).** To 100 mg (0.27 mmol) of **3a** in 3 mL of dry dichloromethane at 20 °C were added 78 mg (0.52 mmol) of *tert*-butyldimethylsilyl chloride and 50 $\mu$L of triethylamine. After 20 h, the mixture was flash chromatographed (10 g of silica gel, 2 × 3 cm column, 10% EtOAc–hexane, 5-mL fractions) to afford 60 mg (57% based on recovered **3a**) of **14**, 20 mg of **3a**, and 65 mg of bissilylated product **16**. The desired monosilylated product **14** is a solid: mp 128–133 °C dec (sealed tube); IR ($CCl_4$) 3316, 2919, 1617, 1591, 1509, 1294, 1254, 1201, 1127, 1099, 1055, 994, 846 cm$^{-1}$; $^1$H NMR $\delta$ 0.10 (s, 6 H), 0.99 (s, 9 H), 1.70 (s, 3 H), 1.80 (s, 3 H), 2.84 (dd, 1 H, $J$ = 10, 16 Hz), 3.04 (dd, 1 H, $J$ = 6, 16 Hz), 3.30 (d, 2 H, $J$ = 7 Hz), 3.45 (br m, 1 H), 3.74 (s, 3 H), 3.80 (s, 3 H), 4.06 (t, 1 H, $J$ = 12 Hz), 4.34 (br d, 1 H, $J$ = 10 Hz), 4.96 (s, 1 H), 5.22 (t, 1 H, $J$ = 7 Hz), 6.28 (s, 1 H), 6.32 (d, 1 H, $J$ = 3 Hz), 6.44 (dd, 1 H, $J$ = 3, 8 Hz), 6.99 (d, 1 H, $J$ = 8 Hz); $R_f$(**14**) 0.27, $R_f$(**16**) 0.58 (silica gel, 10% EtOAc–hexane). Anal. Calcd for (**14**) $C_{28}H_{40}O_5Si$: C, 69.38; H, 8.32. Found: C, 69.25; H, 8.24.

**6-[3,4-Dihydro-5,7-dimethoxy-6-(3-methyl-2-butenyl)-2*H*-1-benzopyran-3-yl]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-(3-methyl-2-butenyl)phenol (15).** To 45 mg (0.095 mmol) of **14** in 2 mL of freshly distilled toluene at −78 °C was added 48 $\mu$L (0.12 mmol) of a 2.5 M solution of *n*-butyllithium in hexane. After the mixture was stirred at −78 °C for 15 min, 30 $\mu$L (0.25 mmol) of 2,2-dimethylallyl bromide was added, and the red mixture was allowed to warm to 20 °C. The mixture, protected from light by aluminum foil, was stirred at 20 °C for 18 h. During this time the color was discharged. The solvent was removed in vacuo at 20 °C, and the residue was introduced onto two preparative (1000-$\mu$m) silica gel plates. The plates were eluted with 15% EtOAc–hexane, and the band with an $R_f$ of 0.62 was extracted to afford 22 mg (48% based on 6 mg of recovered **14**) of product as an oil: IR (film) 3406, 2910, 1609, 1583, 1485, 1252, 1200, 1129, 1102, 1050, 910, 842, 783 cm$^{-1}$; $^1$H NMR $\delta$ 0.20 (s, 6 H), 1.0 (s, 9 H), 1.67 (s, 3 H), 1.77 (s, 3 H), 1.78 (s, 3 H), 1.84 (s, 3 H), 2.80 (dd, 1 H, $J$ = 10, 16 Hz), 3.00 (dd, 1 H, $J$ = 5, 16 Hz), 3.29 (d, 2 H, $J$ = 6 Hz), 3.2–3.5 (br m, 1 H), 3.45 (d, 2 H, $J$ = 6 Hz), 3.72 (s, 3 H), 3.77 (s, 3 H), 4.01 (t, 1 H, $J$ = 10 Hz), 4.32 (d, 1 H, $J$ = 8 Hz), 5.21 (m, 2 H), 5.60 (s, 1 H), 6.26 (s, 1 H), 6.42 (d, 1 H, $J$ = 8 Hz), 6.86 (d, 1 H, $J$ = 8 Hz); $R_f$(**15**) 0.45 (silica gel, 10% EtOAc–hexane); exact mass calcd for $C_{33}H_{48}O_5Si$ 552.3271, found 552.3265.

**(±)-5-*O*-Methyllicoricidin (1).** To 9 mg (0.016 mmol) of **15** in 2 mL of dry THF was added 600 $\mu$L of a solution of pyridine–hydrogen fluoride complex in THF.[11] The mixture was stirred under nitrogen at 20 °C for 28 h. The reaction was then quenched with 5 mL of water and extracted with ethyl acetate. The organic extracts were combined, dried ($MgSO_4$), and evaporated in vacuo to afford 9 mg of unpurified product. Preparative TLC (2:1 hexane–EtOAc) afforded 6 mg (85%) of **1**, which was in all respects identical with a sample of the natural product provided by Dr. Lam:[1] IR ($CCl_4$) 3430, 2930, 1612, 1588, 1452, 1201, 1129, 1100, 1063, 1030, 899 cm$^{-1}$; $^1$H NMR $\delta$ 1.68 (s, 3 H), 1.78 (s, 3 H), 1.80 (s, 3 H), 1.86 (s, 3 H), 2.80 (dd, 1 H, $J$ = 10.5, 16.5 Hz), 3.03 (ddd, 1 H, $J$ = 2, 3.5, 16.5 Hz), 3.30 (d, 2 H, $J$ = 7.5 Hz), 3.40 (m, 1 H), 3.46 (d, 2 H, $J$ = 6.5 Hz), 3.72 (s, 3 H), 3.79 (s, 3 H), 4.03 (t, 1 H, $J$ = 10.5 Hz), 4.32 (ddd, 1 H, $J$ = 2, 3.5, 10.5 Hz), 4.86 (s, 1 H), 5.24 (m, 2 H), 5.51 (s, 1 H), 6.26 (s, 1 H), 6.39 (d, 1 H, $J$ = 8 Hz), 6.86 (d, 1 H, $J$ = 8 Hz); $R_f$(1) 0.56 (silica gel, 2:1 hexane–EtOAc); exact mass calcd for $C_{27}H_{34}O_5$ 438.2406, found 438.2403.

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(11) Prepared by diluting 1 mL of commercially available (Aldrich) HF–pyridine with 7 mL of THF and 2 mL of dry pyridine.

# Cyanide as an Efficient and Mild Catalyst in the Aminolysis of Esters†

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Cyanide anion was found to be a versatile catalyst in the aminolysis of nonactivated esters. A comparative study on various catalysts, including (dimethylamino)pyridine, 2-hydroxypyridine, imidazole, and sodium cyanide, in the ammonolysis of ethyl (*S*)-1-ethyl-2-pyrrolidinecarboxylate (**1**) in methanol showed sodium cyanide to be the superior catalyst. Furthermore, the reaction was completely stereoconservative; i.e., less than 1% racemization occurred. Cyanide ion also proved to be an efficient catalyst in the transesterification with the solvent. Comparative studies on **1**, ethyl benzoate (**4**), ethyl 3-phenylpropionate (**5**), and ethyl phenoxyacetate (**6**) in aminolysis with ammonia, methylamine, and dimethylamine in methanol showed cyanide to be a general catalyst. The reactivity order for various esters was found to be $MeNH_2 > NH_3 > Me_2NH$.

In connection with a recently developed synthesis of (*S*)-2-(aminomethyl)-1-ethylpyrrolidine from L-proline,[1] we required an efficient stereoconservative[2] conversion of the ethyl ester **1** to the primary amide **2** (eq 1). We report here the finding that cyanide is an efficient, yet mild, catalyst in the aminolysis of aliphatic and aromatic esters with amines in alcoholic solution.

The aminolysis of esters is generally a sluggish reaction unless esters having good leaving groups such as nitro-

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