

Regioselective Cleavage Reaction of the Aromatic Methylenedioxy Ring. V.¹⁾ Cleavage with Sodium Alkoxides—Alcohols, Potassium *tert*-Butoxide—Alcohols, Dimsyl Anion—Methyl Alcohol, Metallic Sodium—Alcohols, and Sodium Cyanide in Dipolar Aprotic Solvents

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The reaction of aromatic methylenedioxy compounds containing electron-withdrawing groups with dimsyl anion—methyl alcohol, potassium *tert*-butoxide—alcohols, and metallic sodium—alcohols in dimethyl sulfoxide (DMSO), and with sodium alkoxides—alcohols in hexamethylphosphoramide, gave 3- and 4-hydroxybenzene derivatives in good yield by regioselective attack of the alkoxide ions on the methylenedioxy ring. The formation mechanism of alkoxide ions and the effect of DMSO in the cleavage reaction of the methylenedioxy ring are discussed on the basis of proton nuclear magnetic resonance (¹H-NMR) spectra. The reactions of aromatic methylenedioxy compounds (3 and 22) with sodium cyanide in dipolar aprotic solvents gave 4-cyano-3-hydroxybenzene derivatives (23 and 24) by regioselective attack of the cyanide ion on the methylenedioxy ring. The reactions of aromatic methylenedioxy compounds (28—30) containing no electron-withdrawing group with MeONa—MeOH in dipolar aprotic solvents gave non-regioselective cleavage products (31 and 34).

Keywords regioselective cleavage reaction; methylenedioxy ring; sodium alkoxide; dimsyl anion; potassium *tert*-butoxide; electron-withdrawing group; cyanide ion; dipolar aprotic solvent

We have previously reported^{1,2)} regioselective 3,4-methylenedioxy ring cleavage reactions in aromatic formyl, nitro and acetyl compounds by sodium alkoxides (RONa)—alcohols [R'OH, R=R' or R≡R', R or R'=methyl (Me), isopropyl (Me₂CH), benzyl (PhCH₂), phenyl (Ph), and 4-methoxyphenyl (4-MeOC₆H₄)] in dimethyl sulfoxide (DMSO), and have reached the following conclusions. 1) The regioselective cleavage reactions of the methylenedioxy ring with RONA—R'OH systems are achieved by the regioselective attack of the nucleophile (R'O[−]) formed from protic solvents (R'OH) by RONA and are accelerated by adding DMSO. Namely, the alkoxide ions (MeO[−], Me₂CHO[−], PhCH₂O[−]) formed from protic solvents attack the carbon atom at C-4 in aromatic methylenedioxy compounds to give 3-hydroxybenzene derivatives, while the phenoxide ions (PhO[−], 4-MeOC₆H₄O[−]) attack the carbon atom of the methylenedioxy group in the compounds to give 4-hydroxybenzene derivatives. 2) The order of reactivity of the protic solvents (R'OH) used in the cleavage reactions is PhOH > 4-MeOC₆H₄OH > MeOH > PhCH₂OH, *i.e.*, the inverse of the order of p*K*_a values of the protic solvents, and when the alcohols (ROH) formed from the sodium alkoxides (RONa) show smaller p*K*_a values than the protic solvents (R'OH) in RONA—R'OH systems, both the alcohols formed from sodium alkoxides and protic solvents act as nucleophilic reagents toward the methylenedioxy ring, as would be expected. Consequently, the alcohols formed from the sodium alkoxides in the cleavage reactions with RONA—R'OH systems must show larger p*K*_a values than the protic solvents if the methylenedioxy ring is to be cleaved only by the protic solvents.

In connection with our studies on the cleavage reactions of the aromatic methylenedioxy ring, we wish to describe herein the regioselective cleavage reactions of the aromatic methylenedioxy ring in compounds containing electron-withdrawing groups with dimsyl anion—MeOH, potassium

tert-butoxide (Me₃COK)—MeOH, and/or metallic sodium—(Na)—R'OH [R'=Me, PhCH₂] in DMSO, as well as with RONA—R'OH (R=R' or R≡R', R or R'=Me, PhCH₂, Ph) in hexamethylphosphoramide (HMPA), and with sodium cyanide (NaCN) in dipolar aprotic solvents, together with the cleavage reactions of the aromatic methylenedioxy ring containing no electron-withdrawing group with MeONa—MeOH in dipolar aprotic solvents.

Cleavage of Aromatic Methylenedioxy Compounds (1—3) with Dimsyl Anion—MeOH, and Me₃COK—R'OH (R'=Me, Ph) in DMSO It is well known³⁾ that a mixture of sodium alkoxide (RONa) and DMSO is excellently suited for the deprotonation of weakly acidic OH, NH and CH bonds. On the other hand, it is also known that the dimsyl anion (MeSOCH₂[−])⁴⁾ prepared from DMSO and a base such as sodium hydride (NaH) acts as a specific deprotonating agent in the Sommelet rearrangement.⁵⁾ This indicates that the cleavage reaction of the methylenedioxy ring with RONA—R'OH—DMSO systems may also be promoted by the formation of dimsyl anion from DMSO and RONA, besides the usual solvent effects of DMSO. However, Kingsbury⁶⁾ has shown that the small amounts of dimsyl anion formed from RONA—DMSO are not kinetically significant since the reaction of 2,4-dinitrochlorobenzene with potassium isopropoxide in 50% DMSO—50% isopropyl alcohol (Me₂CHOH) gives isopropyl 2,4-dinitrophenyl ether and no methylsulfinyl 2,4-dinitrophenyl ether. It is of interest to confirm the formation and action of the dimsyl anion in our cleavage reactions, and so we tried the following cleavage reactions of the methylenedioxy ring. The cleavage reactions of compounds 1—3 with MeOH and dimsyl anion in DMSO at room temperature gave 3-hydroxy-4-methoxybenzene derivatives (4—6) in better yields than those obtained previously by using the MeONa—MeOH—DMSO system,^{2a)} as shown in Table I.

Ledwith and McFarlane⁷⁾ have reported that benzophe-

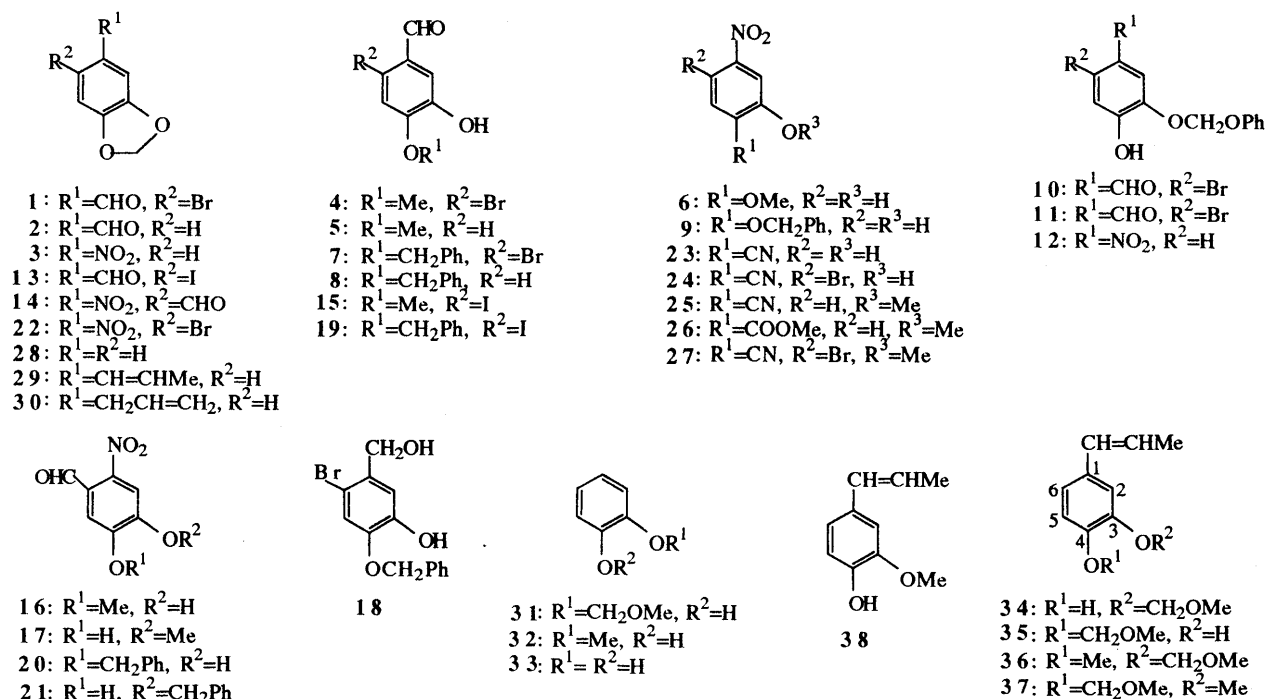
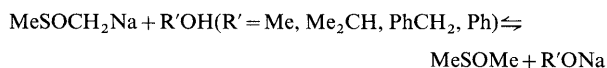


TABLE I. Cleavage of the Methylenedioxy Ring with MeOH and Dimsyl Anion^{a)} or Me₃COK^{b)} in DMSO

Compound (mmol)	Dimsyl anion ^{c)} (ml)	Reaction time (h)	Product	Yield (%)	
				d)	e)
1 ^{a)}	1	3.0	4	75.8	67.0
2 ^{a)}	1	3.0	5	50.8	13.7
3 ^{a)}	1	2.0	6	76.0	73.9
1 ^{b)}	0.44	0.5	4	83.7	67.0
3 ^{b)}	0.50	0.5	6	91.6	73.9

a) Reactions at room temperature in anhydrous MeOH (1.0 ml) and DMSO (1.5 ml). b) Reactions with Me₃COK (1 mmol) and MeOH (0.5 ml) at 50°C in DMSO (0.5 ml). c) The dimsyl anion was prepared from sodium hydride and DMSO in the usual way.⁴⁾ d) Isolation yield. e) Yield of isolated products by R₃ONa and ROH in DMSO.²⁾

none is converted to the benzophenone adduct [(C₆H₅)₂C(OH)CH₂SOMe] by the potassium salt of dimsyl anion formed from Me₃COK–DMSO. We therefore decided to use Me₃COK instead of R₃ONa to promote the formation of the dimsyl anion and alkoxide ions (R'O[−]) in R₃ONa–R'OH–DMSO systems. As shown in Table I, the cleavage reactions of compounds 1 and 3 with MeOH in Me₃COK–DMSO system gave 3-hydroxy-4-methoxybenzene derivatives (4 and 6) in good yields. The above results indicate that the reactivity and formation of alkoxide ions (R'O[−]) in R₃ONa–R'OH–DMSO systems was promoted by the dimsyl anion, which may be formed through an ion-pair such as [RO[−]...S⁺(O[−])Me₂] from R₃ONa and DMSO. However, the pK_a values of DMSO, Me₂CHOH, MeOH, PhCH₂OH, and PhOH are ca. 35, ca. 17, ca. 15, ca. 15, and ca. 10, respectively. If one considers a reaction of the type shown below;



there will be present 1 part in 10²⁰ of MeSOCH₂Na in the case of MeOH and 1 part in 10²⁵ of MeSOCH₂Na in the

case of PhOH. Consequently, MeSOCH₂Na will play no significant part in the cleavage reactions even though it may be responsible for the observed exchange reactions. Hence, we tried to confirm the possibility of formation of the dimsyl anion in the R₃ONa–ROH (R = Me, PhCH₂)–deuterium dimethyl sulfoxide (*d*₆–DMSO, O=S(CD₃)₂) system by proton nuclear magnetic resonance (¹H-NMR) spectroscopy.^{8a)} For example, the ¹H-NMR spectrum of a mixture of MeONa (24.4 mg)–MeOH (0.5 ml) stirred for 70 s at room temperature, showed broad singlet signals of the methyl (δ 3.05) and hydroxyl protons (δ 5.80) of MeOH, which indicated the presence of a strong solvent–anion hydrogen bond, such as [MeO[−]...H–OMe]. The ¹H-NMR spectrum of a mixture of MeOH (0.5 ml) and *d*₆–DMSO (0.5 ml) stirred for 70 s at 170°C, showed a quartet signal [δ 4.04 (*J*=6.0 Hz)] due to the hydroxyl proton and a doublet signal [δ 3.10 (*J*=6.0 Hz)] due to methyl protons of MeOH, which indicated the presence of hydrogen bonds such as [MeO–H...O=S(CD₃)₂]. The ¹H-NMR spectrum of a mixture of MeOH (0.5 ml), MeONa (24.4 mg) and *d*₆–DMSO (0.5 ml) stirred for 70 s or for 90 min at room temperature showed the usual MeOH signals [δ 3.07 (3H, s, OMe) and δ 4.57 (1H, s, OH)]^{8b)} together with disappearance of hydrogen bond signals [MeO–H...O=S(CD₃)₂] between MeOH and *d*₆–DMSO. The above results indicated that the methoxide ions are strongly solvated in MeOH, but are less solvated in *d*₆–DMSO. The ¹H-NMR spectrum of a mixture of MeOH (0.5 ml), MeONa (24.4 mg) and *d*₆–DMSO (0.5 ml) stirred for 70 s at 170°C showed small multiplet signals due to the dimethyl moiety of DMSO at δ 2.45 (ca. 0.1H) together with MeOH signals [δ 3.13 (3H, s, OMe) and δ 4.89 (ca. 0.9H, s, OH)]. This shows that the deuterium protons of *d*₆–DMSO were exchanged in part with the hydroxyl proton of MeOH, yielding a small quantity of dimsyl anion from the MeONa–MeOH–*d*₆–DMSO system as deduced. Consequently, the effects of DMSO on the cleavage reaction are thought to be as follows. Although the cleavage reactions are promoted in part by

TABLE II. Cleavage of the Methylenedioxy Ring with R'ONa and R'OH in HMPA

Compound (1 mmol)	R in R'ONa (mmol)		R' in R'OH (ml)		HMPA (ml)	Conditions		Product	Yield (%)	
						Time (min)	Temp (°C)		a)	b)
1	Me	2.5	Me	1.0	2.5	9	150	4	79.6	67.0
2	Me	2.5	Me	1.0	2.5	9	150	5	62.6	13.7
3	Me	2.5	Me	1.0	2.5	9	150	6	94.6	73.9
1	PhCH ₂	2.5	PhCH ₂	1.0	2.5	9	150	7	32.1	25.0
2	PhCH ₂	2.5	PhCH ₂	1.0	2.5	1.4	150	8	25.0	23.0
3	PhCH ₂	2.5	PhCH ₂	1.0	2.5	1.5	150	9	32.0	54.0
1	Me	2.5	PhCH ₂	1.0	2.5	9	150	7	42.0	
2	Me	2.5	PhCH ₂	1.0	2.5	1.4	150	8	26.0	
3	Me	2.5	PhCH ₂	1.0	2.5	1.4	150	9	37.0	27.0
1	Ph	2.5	Ph	1.5	2.5	20	150	10	47.0	55.7
2	Ph	2.5	Ph	1.5	2.5	50	150	11	14.6	16.6
3	Ph	2.5	Ph	1.5	2.5	25	150	12	56.4	43.6
2	Me	2.5	Ph	1.1	2.5	50	150	11	30.5	12.6
3	Me	2.5	Ph	1.1	2.5	25	170	12	58.7	

a) Isolation yield. b) Yield of isolated products by R'ONa-R'OH in DMSO.²⁾

the formation of a small quantity of dimsyl anion that is not kinetically significant, the big difference in activity for the alkoxide ions (R'O⁻) formed from R'OH in the two solvent systems (R'ONa-R'OH and R'ONa-R'OH-DMSO) is attributed to the presence of strong solvent-anion hydrogen bonds in R'OH (RO⁻...H-OR ⇌ RO-H...⁻OR') that are almost absent in DMSO, as observed in nucleophilic aromatic substitution reactions.^{6,9)} This conclusion was supported by the results of the cleavage reactions of aromatic methylenedioxy compounds with R'ONa-R'OH-HMPA systems.

Cleavage of Aromatic Methylenedioxy Compounds (1—3) with R'ONa (R=Me, PhCH₂, Ph)-R'OH (R'=Me, PhCH₂, Ph) in HMPA The above consideration of DMSO effects in the cleavage reactions indicates that the cleavage reactions of the methylenedioxy ring by R'ONa-R'OH will be promoted on changing from protic solvents (R'OH) to dipolar aprotic solvents. Thus, we tried the cleavage reaction with R'ONa-R'OH in HMPA (dipolar aprotic solvent), since it is well known¹⁰⁾ that HMPA promotes the ionization of hydrocarbons, and that the hydrogen of HMPA is completely unreactive to base.

As was expected, the cleavage reactions of compounds 1—3 with R'ONa-R'OH (R=R' or R≠R', R or R'=Me, PhCH₂, Ph) in HMPA gave 3-hydroxybenzene derivatives (4—9),²⁾ and 4-hydroxybenzene derivatives (10—12),^{1,2b)} respectively, in good yields as shown in Table II. In particular, the cleavage reactions of compounds 1—3 with MeONa-MeOH in HMPA were more useful than those with MeONa-MeOH in DMSO.

Cleavage of Aromatic Compounds (1—3, 13, 14) with Na-MeOH or PhCH₂OH in DMSO In the cleavage reaction of the methylenedioxy ring with R'ONa-R'OH-DMSO (R=R' or R≠R', R or R'=Me, PhCH₂) systems, R'ONa used as the base must be prepared from ROH and Na under the anhydrous conditions, and must satisfy the requirement that the alcohols (ROH) formed from R'ONa show larger pK_a values than the protic solvents (R'OH) in the case of R=R', as described in this paper. Hence, we decided to use Na as a base instead of R'ONa in the cleavage reactions. The reactions of compounds 1—3, 13 and 14 with Na-MeOH or Na-PhCH₂OH in DMSO gave 3-hydro-

TABLE III. Cleavage of the Methylenedioxy Ring with Sodium Metal (Na) and ROH in DMSO

Starting material (1 mmol)	Conditions ^{a)}	Product	Yield (%)	
			b)	c)
1	A	4	58.3	67.0
2	A	5	25.4	13.7
3	A	6	80.7	73.9
13	A	15	37.6	44.4
14	A	16	66.1	50.8
		17	3.0	25.0
1	B	7	17.9	25.0
1	B	18	14.2	
2	B	8	9.5	23.0
3	B	9	72.4	54.0
13	B	19	12.0	14.0
14	B	20	50.4	41.0
		21	6.3	

a) A, Reactions with Na (2 mmol) and anhydrous MeOH (2 ml) in DMSO (1.5 ml) at 150 °C for 3.5 min; B, Reactions with Na (2 mmol) and anhydrous PhCH₂OH (1.0 ml) in DMSO (1.5 ml) at room temperature for 20 h. b) Isolation yield. c) Yields of isolated products by R'ONa and ROH in DMSO.²⁾

TABLE IV. Cleavage of the Methylenedioxy Ring with Sodium Cyanide

Compound (1 mmol)	Solvent (ml)	Sodium cyanide (mmol)	Conditions		Product	Yield (%) ^{a)}
			Time	Temp. (°C)		
3	DMSO	1.5	1.0	30 min	150	23
	DMF	1.5	1.0	30 min	150	23
	HMPA	2.0	2.5	9 min	150	23
	MeOH	1.5	1.0	35 h	80	4
22	DMSO	1.5	1.0	2 min	150	24
	DMF	1.5	1.0	2.5 h	150	24
	HMPA	2.0	2.5	35 min	150	24

a) Isolation yield.

xybenzene derivatives (4—6 and 15—17 or 7—9 and 18—21), as shown in Table III. This method is convenient, and the yields of 6 and 9 obtained by the cleavage reaction of 3 were increased compared with those obtained previously²⁾ by using R'ONa-ROH (R=Me, PhCH₂)-

TABLE V. Cleavage of **28**, **29** and **30** with MeONa and MeOH in HMPA or DMSO^{a)}

Compound (1 mmol)	13.5% MeONa in MeOH (ml)	HMPA (ml)	DMSO (ml)	Product	Yield (%) ^{b)}
28	1.0	1.5		31	61.7
28	1.0		1.5	31	22.0
28	2.5			No reaction	
29	1.0	1.5		(34 + 35) ^{c)}	63.7
29	1.0		1.5	(34 + 35) ^{d)}	20.4
29	2.5			(34 + 35)	2.5
30	1.0	1.5		(34 + 35) ^{e)}	61.5
30	1.0		1.5	(34 + 35) ^{f)}	38.8
30	2.5			(34 + 35)	0.7

a) The reaction was carried out for 2 h at 150 °C. b) Isolation yield. c–f) An inseparable mixture of **34** and **35**. c), ca. 1.0:1.5; d), ca. 4.0:1.0; e), ca. 1.0:1.5; f), ca. 1.6:1.0.

DMSO systems.

Cleavage of Aromatic Methylenedioxy Compounds (3**, **22**) with NaCN in Dipolar Aprotic Solvents** We planned the regioselective cleavage reaction of aromatic methylenedioxy compounds with the cyanide ion (CN[−]) instead of the alkoxide ion to give cyanobenzene compounds, which can easily be converted to amino, carboxyl, carbonyl and ester compounds. In dipolar aprotic solvents [DMSO, *N,N*-dimethyl formamide (DMF), HMPA], the reaction of compounds **3** and **22** with NaCN gave phenolic compounds [**23** (C₇H₄N₂O₃, mp 155–156 °C) and **24** (C₇H₃BrNO₃, mp 300 °C)], respectively, as shown in Table IV, and the best result was obtained in HMPA. Compounds **23** and **24** were established to be 4-cyano-3-hydroxynitrobenzene and 6-bromo-4-cyano-3-hydroxynitrobenzene, respectively, by chemical transformation, and from physical and spectral data, as described in Experimental. On the other hand, the reaction of **3** with NaCN in MeOH gave only **6** in 16.1% yield instead of **23**, by attack of the methoxide ion on the methylenedioxy ring.

Cleavage of Aromatic Methylenedioxy Compounds (28**–**30**) with MeONa–MeOH in HMPA or DMSO** We have already reported^{1,2)} the regioselective cleavage of 3,4-methylenedioxy aromatic compounds containing electron-withdrawing groups with R₂ONa–R'OH in dipolar aprotic solvents. Therefore, we carried out the cleavage reaction of aromatic methylenedioxy compounds (**28**–**30**) containing no electron-withdrawing group with MeONa–MeOH in HMPA or DMSO as shown in Table V.

The reaction of compounds **28**–**30** with MeONa–MeOH in HMPA or DMSO gave phenolic products (**31** from **28** and an inseparable mixture of **34** and **35** from **29** or **30**), and the best result was obtained in HMPA. The infrared (IR) spectrum of **31** (C₈H₁₀O₃) showed absorption due to a hydroxy group at 3400 cm^{−1}, and the ¹H-NMR (CDCl₃) spectrum showed the presence of a methoxy group at δ 3.46 (3H, s, OCH₂OMe), a methylenedioxy group at δ 5.12 (2H, s, OCH₂OMe), a hydroxy group at δ 6.07 (1H, s, OH, deformed with D₂O), and aromatic protons at δ 6.99 (4H, m). Consequently, compound **31** was established to be 2-methoxymethoxyphenol, which can easily be converted to 2-methoxyphenol (**32**) and 1,2-dihydroxybenzene (**33**). As shown in Table V, phenolic compounds (C₁₁H₁₄O₃) formed from **29** or **30** were assigned as an inseparable

mixture of 4-hydroxy-3-methoxymethoxy-1-methylvinylbenzene (**34**) and 3-hydroxy-4-methoxymethoxy-1-methylvinylbenzene (**35**) on the basis of chemical transformation, and physical and spectral data (see Experimental). Treatment of the phenolic compounds (**34** and **35**) formed from **29** with diazomethane in diethyl ether gave an inseparable mixture (ca. 1.0:1.4) of the methyl ether derivatives (**36** and **37**), which were identified from a comparison of the ¹H-NMR spectrum with that of 3-methoxy-4-methoxymethoxy-1-methylvinylbenzene (**37**) prepared by methoxymethylation of isoeugenol (**38**) with methoxymethyl chloride (MeOCH₂Cl) (see Experimental). On the other hand, the reactions of compounds **28**–**30** with MeONa–MeOH in the absence of dipolar aprotic solvents gave essentially only the starting materials. Although the cleavage reaction of the aromatic methylenedioxy ring containing no electron-withdrawing group with MeONa–MeOH was promoted by addition of HMPA or DMSO, the reaction was nonregioselective. We are now trying to synthesize some biologically active compounds by this method.

Experimental

Melting points were determined by the capillary method and were not corrected. ¹H-NMR spectra were measured on a JEOL PS-100 or a JEOL JNM-FX-200 spectrometer using tetramethylsilane as an internal standard. IR spectra were recorded on a Hitachi 215 IR spectrophotometer. Mass spectra (MS) were taken with a JEOL JMS-D-300 mass spectrometer. Analytical thin layer chromatography (TLC) was performed on precoated glass plates with Merck Kieselgel 60F₂₅₄ as the adsorbent. After development, the plates were air-dried, and exposed to ultraviolet (UV) light and/or sprayed with 1% cerium sulfate in 10% aqueous sulfuric acid, and heated. Preparative TLC (P-TLC) was performed on 20 × 20 cm glass plates coated with Merck Kieselgel 60PF₂₅₄ as the adsorbent (20 g per sheet). Column chromatography was performed on Merck Kieselgel 60 (70–230 mesh). Solvents were purified and dried by standard methods.

Cleavage of 6-Bromopiperonal (1**) with MeOH and Dimsyl Anion in DMSO** Dimsyl anion was prepared from DMSO (10 ml) and sodium hydride (550 mg) in the usual way.⁴⁾ A mixture of dimsyl anion (3 ml) and MeOH (2 ml) was stirred at room temperature for 10 min under nitrogen. A solution of **1** (229 mg, 1 mmol) in MeOH (1 ml) was added slowly to the reaction mixture, and the whole was further stirred at room temperature for 13 h. The reaction mixture was diluted with cold water (40 ml) and 10% NaOH (10 ml), and extracted with diethyl ether (50 ml × 2). Piperonyl alcohol (25 mg, 10.8%) was isolated from the extract. The mother liquor was acidified (pH 4–5) with concentrated HCl, and extracted with diethyl ether (50 ml × 3). The extract was washed with water, dried (MgSO₄), and evaporated. The residue was purified by P-TLC (eluent benzene–acetone, 4:1) to give 6-bromoisovaniline (**4**, 175 mg, 75.8%), mp 107–110 °C, which was identical with authentic **4**.^{2a)} Compounds **2** and **3** were cleaved similarly, as shown in Table I.

Cleavage of **1 with Me₃COK and MeOH in DMSO** A mixture of Me₃COK (112.2 mg, 1 mmol) and DMSO (0.5 ml) was stirred at 50 °C for 30 min, and then MeOH (0.5 ml) was added. The mixture was stirred at 50 °C for 30 min, then **1** (100 mg, 0.44 mmol) was added, and stirring was continued at 50 °C for 30 min. Work-up in the usual way gave **4** (83.7 mg, 83.0%), mp 104–107 °C.^{2a)} Compound **3** was cleaved similarly, as shown in Table I.

Cleavage of **1 with MeONa and MeOH in HMPA** A mixture of **1** (229 mg, 1 mmol), MeONa (135 mg, 2.5 mmol), and MeOH (1.0 ml) in HMPA (2.5 ml) was stirred at 150 °C for 9 min. The reaction mixture was poured into cold water (20 ml), NaOH (30 mg) was added, and the whole was extracted with diethyl ether (50 ml × 2). Piperonyl alcohol (5 mg, 2.2%) was isolated from the extract. The mother liquor was acidified (pH 4–5) with concentrated HCl, and extracted with diethyl ether (50 ml × 3). The extract was washed with water, dried (MgSO₄), and evaporated. The residue was purified by P-TLC (eluent benzene–acetone, 4:1) to give **4** (183.9 mg, 79.6%), mp 105–108 °C.^{2a)} Compounds **2** and **3** were cleaved similarly, as shown in Table II.

Cleavage of **1 with PhCH₂ONa and PhCH₂OH in HMPA** A mixture

of **1** (229 mg, 1 mmol), PhCH_2ONa (325 mg, 2.5 mmol), and PhCH_2OH (1.0 ml) in HMPA (2.5 mmol) was stirred at 150 °C for 9 min. Work-up in the usual way gave **7** (98.8 mg, 32.1%), mp 123–129 °C.²⁾ Compounds **2** and **3** were cleaved similarly, as shown in Table II.

Cleavage of 1 with MeONa and PhCH₂OH in HMPA A mixture of **1** (229 mg, 1 mmol), MeONa (135 mg, 2.5 mmol), and PhCH_2OH (1.0 ml) in HMPA (2.5 ml) was stirred at 150 °C for 9 min. Work-up in the usual way gave 4-benzyloxy-6-bromo-3-hydroxybenzaldehyde (**7**, 129.2 mg, 42.0%), mp 128–129 °C, which was identical with authentic **7**.^{2c)} Compounds **2** and **3** were cleaved similarly, as shown in Table II.

Cleavage of 1 with PhONa and PhOH in HMPA A mixture of **1** (229 mg, 1 mmol), PhONa (290 mg, 2.5 mmol), and PhOH (1.5 ml) in HMPA (2.5 ml) was stirred at 150 °C for 20 min. Work-up in the usual way gave 6-bromo-4-hydroxy-3-phenoxy-methoxybenzaldehyde (**10**, 66.8 mg, 47.0%, mp 119–120 °C, from petroleum ether–diethyl ether), which was identical with authentic **10**.^{2b)} Compounds **2** and **3** were cleaved similarly, as shown in Table II.

Cleavage of Piperonal (2) with MeONa and PhOH in HMPA A mixture of **2** (150 mg, 1 mmol), MeONa (135 mg, 2.5 mmol), and PhOH (1.1 ml) in HMPA (2.5 ml) was stirred at 150 °C for 50 min. Work-up in the usual way gave 4-hydroxy-3-phenoxy-methoxybenzaldehyde (**11**, 43.3 mg, 30.5%), mp 115–118 °C (petroleum ether–diethyl ether), which was identical with authentic **11**.^{2b)} Compound **3** was cleaved similarly, as shown in Table II.

Cleavage of 1 with Na and MeOH in DMSO Na (46 mg, 2 mmol) was added to a solution of **1** (229 mg, 1 mmol) and MeOH (2 ml) in DMSO (1.5 ml), and the mixture was stirred at 150 °C for 3.5 min. MeOH was removed under reduced pressure, and the residue thus obtained was diluted with cold water (20 ml) and 10% NaOH (10 ml). Work-up in the usual way gave **4** (134.6 mg, 58.3%), mp 108–109 °C.^{2a)} Compounds **2**, **3**, and **13–14** were cleaved similarly, as shown in Table III.

Cleavage of 1 with Na and PhCH₂OH in DMSO A mixture of **1** (229 mg, 1 mmol), Na (46 mg, 2 mmol) and benzyl alcohol (1 ml) in DMSO (1.5 ml) was stirred at room temperature for 20 h. Work-up in the usual way gave **7** (54.9 mg, 17.9%), mp 127–129 °C and 4-benzyloxy-6-bromo-3-hydroxybenzyl alcohol (**18**, 43.8 mg, 14.2%), mp 147–149 °C, which were identical with authentic samples **7**^{2b)} and **18**^{2b)} Compounds **2**, **3**, **13**, and **14** were cleaved similarly, as shown in Table III.

Cleavage of 3 with Sodium Cyanide in Dipolar Aprotic Solvents (i) In DMSO: A mixture of **3** (167 mg, 1 mmol) and NaCN (49 mg, 1 mmol) in DMSO (1.5 ml) was stirred at 150 °C for 30 min. The mixture was diluted with cold water (10 ml), and 5% NaOH (10 ml), then extracted with diethyl ether (50 ml × 2). The ether extract was purified by P-TLC (eluent CHCl_3) to give the starting material **3** (38.5 mg, 23.2%). The mother liquor was acidified (pH 4–5) with concentrated HCl and extracted with diethyl ether (50 ml × 3). The extract was washed with water, dried (MgSO_4), and evaporated. The residue was purified by P-TLC (eluent CHCl_3 –MeOH, 7:1) to give 4-cyano-3-hydroxynitrobenzene (**23**, 31.3 mg, 19.6%), mp 155–156 °C (from CCl_4). IR ν_{max} cm^{-1} : 3280 (OH), 2240, 1620 (CN), 1535, 1355 (NO_2). ¹H-NMR (100 MHz, CDCl_3) δ : 6.91 (1H, d, J = 8 Hz, 5-H), 7.77 (1H, d, J = 2 Hz, 2-H), 7.83 (1H, dd, J = 8.0, 2.0 Hz, 6-H). Anal. Calcd for $\text{C}_7\text{H}_4\text{N}_2\text{O}_3$: C, 51.12; H, 2.46; N, 17.02. Found: C, 51.15; H, 2.43; N, 17.01.

(ii) In HMPA: A mixture of **3** (167 mg, 1 mmol) and NaCN (49 mg, 1 mmol) in HMPA (2 ml) was stirred at 150 °C for 1 min. Further NaCN (24.5 mg, 0.5 mmol × 3) was then added to the mixture every 1 min for 3 min under stirring at 150 °C. Work-up of the mixture as described in (i) gave **23** (148.3 mg, 90.4%), mp 156–157 °C.

(iii) In DMF: A mixture of **3** (167 mg, 1 mmol) and NaCN (49 mg, 1 mmol) in DMF (1.5 ml) was stirred at 150 °C for 30 min. Work-up of the mixture as described in (i) gave **23** (27.2 mg, 16.1%), mp 156–158 °C and unchanged starting material **3** (99.9 mg, 59.1%).

Cleavage of 3 with Sodium Cyanide in MeOH A mixture of **3** (167 mg, 1 mmol) and NaCN (49 mg, 1 mmol) in MeOH (1.5 ml) was stirred at 80 °C for 35 h. Work-up in the usual way gave **4** (27.2 mg, 16.1%), mp 107–109 °C²⁾ and unchanged starting material **3** (99.9 mg, 59.1%).

4-Cyano-3-methoxynitrobenzene (25) Compound **23** (24.7 mg, 0.15 mmol) was methylated with ethereal diazomethane to give **25** (16.4 mg, 61.2%), mp 175–177 °C (from ethyl acetate, lit.¹¹⁾ mp 180 °C). IR ν_{max} cm^{-1} : 2230, 1615 (CN), 1535, 1355 (NO_2). ¹H-NMR (100 MHz, d_6 -acetone) δ : 4.20 (3H, s, 3-OMe), 8.12 (3H, s, 2, 5, 6-H).

4-Carbomethoxy-3-methoxynitrobenzene (26) Dry hydrogen chloride gas was introduced into a mixture of **25** (36.3 mg, 0.2 mmol), dry MeOH (3 ml) and dry ether (3 ml) for 2 h. The mixture was allowed to stand for 12 h at room temperature, and then treated with water (20 ml), heated at 60 °C for 30 min, and extracted with CHCl_3 . The extract was washed with

water, dried (MgSO_4), and evaporated. The white residue was purified by P-TLC (eluent CHCl_3) to give **26** (15.8 mg, 37.4%), mp 86–88 °C (from MeOH, lit.¹²⁾ mp 86.5–87.1 °C). IR ν_{max} cm^{-1} : 1740, 1530, 1355 (NO_2). ¹H-NMR (100 MHz, CDCl_3) δ : 3.98 (3H, s, 3-OMe), 4.05 (3H, s, 4-COOMe), 7.85 (3H, s, 2, 5, 6-H).

Cleavage of 6-Bromo-3,4-methylenedioxy-nitrobenzene (22) with NaCN in DMSO A mixture of **22** (244 mg, 1 mmol) and NaCN (49 mg, 2 mmol) in DMSO (1.5 ml) was stirred at 150 °C for 2 min. After usual work-up, the reaction mixture was purified by P-TLC (eluent CHCl_3 –MeOH, 10:3) to give a 6-bromo-4-cyano-3-hydroxynitrobenzene (**24**, 22.5 mg, 5.5%), and unchanged starting material **22** (108.6 mg, 44.5%). Compound **24** had mp 300 °C (from CHCl_3 –MeOH). IR ν_{max} cm^{-1} : 3400 (OH), 2245, 1620 (CN), 1530, 1355 (NO_2). ¹H-NMR (100 MHz, CD_3OD) δ : 7.15 (1H, m, OH), 7.80 (2H, brs, 2 and 5-H). Anal. Calcd for $\text{C}_7\text{H}_3\text{BrNO}_3$: C, 34.60; H, 1.24; N, 11.53. Found: C, 34.80; H, 1.25; N, 11.46.

Compound **22** was also similarly cleaved with NaCN in DMF and/or HMPA, as shown in Table IV.

6-Bromo-4-cyano-3-methoxynitrobenzene (27) A solution of **24** (22.5 mg, 0.1 mmol) in MeOH (5 ml) was treated with ethereal diazomethane, and allowed to stand at room temperature for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by P-TLC (eluent CHCl_3 –benzene, 10:1) to give **27** (12.0 mg, 52.6%), mp 203–205 °C (from *n*-hexane– CHCl_3). IR ν_{max} cm^{-1} : 2240, 1620 (CN), 1540, 1365 (NO_2). ¹H-NMR (100 MHz, CDCl_3) δ : 3.92 (3H, s, 3-OMe), 7.37 (1H, s, 2-H), 7.87 (1H, s, 5-H). The ¹H-NMR spectrum of **27** showed an intramolecular nuclear Overhauser effect (NOE) increment of 22% between the methoxy protons (δ 3.92) and H-2 (δ 7.37).

Cleavage of 1,2-Methylenedioxybenzene (28) with MeONa and MeOH in Dipolar Aprotic Solvents (i) In HMPA: A mixture of **28** (122.0 mg, 1 mmol) and 13.5% MeONa–MeOH (1 ml) in HMPA (1.5 ml) was stirred at 150 °C for 2 h. The mixture was diluted with cold water (30 ml), 10% NaOH (20 ml), and extracted with diethyl ether (30 ml × 2). The ether extract was purified by P-TLC (eluent benzene) to give the starting material **28** (21.5 mg, 17.6%). The mother liquor was acidified (pH 5–6) with concentrated HCl and extracted with diethyl ether (40 ml × 3). The extract was washed with water, dried (MgSO_4), and evaporated. The residue was purified by P-TLC (eluent benzene) to give 2-methoxymethoxyphenol (**31**, 95.0 mg, 61.7%, yellow oil). IR ν_{max} cm^{-1} : 3425 (OH). ¹H-NMR (100 MHz, CDCl_3) δ : 3.46 (3H, s, OCH_2OMe), 5.17 (2H, s, OCH_2OMe), 5.97 (1H, br s, OH, deformed with D_2O), 6.85 (4H, m, aromatic H). High-resolution MS: Calcd for $\text{C}_8\text{H}_{10}\text{O}_3$: 154.0629. Found: 154.0669.

(ii) In DMSO: A mixture of **28** (122 mg, 1 mmol) and 13.5% MeONa–MeOH (1.5 ml) in DMSO (1.5 ml) was stirred at 150 °C for 2 h. Work-up of the mixture as described in (i) gave **28** (40.3 mg, 33.0%) and **31** (44.8 mg, 30.0%).

(iii) In MeOH: A mixture of **28** (122 mg, 1 mmol) and 13.5% MeONa–MeOH (1.5 ml) was stirred at 150 °C for 2 h. Work-up of the mixture as described in (i) gave only **28** (83.5 mg, 68.4%).

Cleavage of Isosafrol (29) with MeONa and MeOH in Dipolar Aprotic Solvents (i) In HMPA: A mixture of **29** (162.0 mg, 1 mmol) and 13.5% MeONa–MeOH (1 ml) in HMPA (1.5 ml) was stirred at 150 °C for 2 h. The mixture was diluted with cold water (30 ml), and 10% NaOH (20 ml), then extracted with diethyl ether (30 ml × 2). The ether extract was purified by P-TLC (eluent CHCl_3) to give the starting material **29** (25.1 mg, 15.5%). The mother liquor was acidified (pH 5–6) with concentrated HCl and extracted with diethyl ether (40 ml × 3). The extract was washed with water, dried (MgSO_4), and evaporated. The residue was purified by P-TLC (eluent CHCl_3 ; R_f = 0.30–0.48) to give an inseparable mixture (132.5 mg, 63.7%, yellow oil, ca. 1.0:1.5) of phenolic compounds (**34** and **35**), which were identified from the ¹H-NMR spectral data. IR ν_{max} cm^{-1} : 3430 (OH). ¹H-NMR (200 MHz, CDCl_3) δ : 1.82, 1.83 (totally 3H, each d, J = 6.0 Hz, $\text{CH}=\text{CHMe}$), 3.48, 3.49 (ca. 1.0:1.5, totally 3H, each s, OCH_2OMe), 5.14, 5.17 (ca. 1.0:1.5, totally 2H, each s, OCH_2OMe), 6.01, 6.05 (totally 1H, m, $\text{CH}=\text{CHMe}$), 6.29 (1H, d, J = 14.0 Hz, $\text{CH}=\text{CHMe}$), 6.75, 6.87 (totally 1H, each dd, J = 1.7, 8.3 Hz, 6-H), 6.87, 6.98 (totally 1H, each d, J = 8.3 Hz, 5-H), 6.95, 7.08 (totally 1H, each d, J = 1.7 Hz, 2-H). High-resolution MS: Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3$: 194.0941. Found: 194.0914.

(ii) In DMSO: A mixture of **29** (162 mg, 1 mmol) and 13.5% MeONa–MeOH (1.5 ml) in DMSO (1.5 ml) was stirred at 150 °C for 2 h. Work-up of the mixture as described in (i) gave **29** (17.1 mg, 10.6%) and phenolic compounds (39.6 mg, 20.4%). The phenolic compounds were identified as an inseparable mixture (ca. 4.0:1.0) of **34** and **35** from the ¹H-NMR spectral data. IR ν_{max} cm^{-1} : 3420 (OH). ¹H-NMR (100 MHz, CDCl_3) δ : 1.83 (3H, d, J = 6.2 Hz, $\text{CH}=\text{CHMe}$), 3.50 (3H, s, OCH_2OMe), 5.15, 5.16 (ca. 4.0:1.0, totally 2H, each s, OCH_2OMe), 6.08 (1H, m,

CH=CHMe), 6.30 (1H, d, $J=14.5$ Hz, CH=CHMe), 6.74, 6.84 (totally 1H, each dd, $J=1.7, 8.0$ Hz, 6-H), 6.89, 6.98 (totally 1H, each d, $J=8.0$ Hz, 5-H), 6.96, 7.06 (totally 1H, each d, $J=1.7$ Hz, 2-H). High-resolution MS: Calcd for $C_{11}H_{14}O_3$: 194.0941. Found: 194.0933.

(iii) In MeOH: A mixture of **29** (162 mg, 1 mmol) and 13.5% MeONa–MeOH (2.5 ml) was stirred at 150 °C for 2 h. Work-up of the mixture as described in (i) gave **28** (132.2 mg, 85.5%) and phenolic compounds (4.0 mg, 2.5%).

Conversion of Phenolic Compounds (34 and 35) Formed from 29 to Methyl Ether Derivatives (36 and 37) A solution of **34** (75.4 mg, 0.39 mmol) in MeOH (10 ml) was treated with ethereal diazomethane, and allowed to stand at 10 °C for 60 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by P-TLC (eluent benzene–diethyl ether, 10:1) to give an inseparable mixture (63.8 mg, 73.3%, yellow oil, *ca.* 1.0:1.4) of the methyl ether derivatives (**36** and **37**), which were identified from a comparison of the ^1H -NMR spectrum with that of authentic **37**. IR ν_{max} cm^{-1} : no OH. **36**: ^1H -NMR (200 MHz, CDCl_3) δ : 1.85 (3H, dd, $J=1.4, 6.3$ Hz, CH=CHMe), 3.52 (3H, s, OCH_2OMe), 3.86 (3H, s, 3-OMe), 5.23 (2H, s, OCH_2OMe), 6.09 (1H, dq, $J=6.3, 15.6$ Hz, CH=CHMe), 6.31 (1H, dd, $J=1.4, 15.6$ Hz, CH=CHMe), 6.81 (1H, d, $J=8.3$ Hz, 5-H), 6.93 (1H, dd, $J=2.2, 8.3$ Hz, 6-H), 7.15 (1H, d, $J=2.2$ Hz, 2-H). **37**: ^1H -NMR (200 MHz, CDCl_3) δ : 1.86 (3H, dd, $J=6.4, 1.5$ Hz, CH=CHMe), 3.51 (3H, s, OCH_2OMe), 3.88 (3H, s, 3-OMe), 5.21 (2H, s, OCH_2OMe), 6.11 (1H, dq, $J=6.4, 15.6$ Hz, CH=CHMe), 6.33 (1H, dd, $J=1.5, 15.6$ Hz, CH=CHMe), 6.84 (1H, dd, $J=1.95, 8.5$ Hz, 6-H), 6.90 (1H, d, $J=1.95$ Hz, 2-H), 7.07 (1H, d, $J=8.5$ Hz, 5-H). High-resolution MS: Calcd for $C_{12}H_{16}O_3$: 208.1097. Found: 208.1081.

Conversion of Isoeugenol (38) to 37 A mixture of **38** (1.64 g, 10 mmol), CH_2Cl_2 (20 ml), MeOCH_2Cl (1.5 g, 18.6 mmol) and *N,N*-dimethylaniline (1.45 g, 12 mmol) was stirred at 70 °C for 7 h. The mixture was diluted with cold water (30 ml), 10% NaOH (20 ml), and extracted with diethyl ether (100 ml $\times$ 2). The extract was washed with 5% NaOH (20 ml $\times$ 2) and water (30 ml $\times$ 3), dried (MgSO_4), and evaporated. The residue was chromatographed on silica gel (80 g, eluent, benzene–diethyl ether, 10:0.5) to give **37** (1.3 g, 56.8%, yellow oil). IR ν_{max} cm^{-1} : no OH. ^1H -NMR (200 MHz, CDCl_3) δ : 1.86 (3H, dd, $J=1.46, 6.59$ Hz, CH=CHMe), 3.51 (3H, s, OCH_2OMe), 3.88 (3H, s, 3-OMe), 5.20 (2H, s, OCH_2OMe), 6.11 (1H, dq, $J=6.59, 15.63$ Hz, CH=CHMe), 6.34 (1H, dd, $J=1.46, 15.63$ Hz, CH=CHMe), 6.83 (1H, dd, $J=2.0, 8.3$ Hz, 6-H), 6.89 (1H, d, $J=2.0$ Hz, 2-H), 7.07 (1H, d, $J=8.3$ Hz, 5-H). High-resolution MS: Calcd for $C_{12}H_{16}O_3$: 208.1097. Found: 208.1092.

Cleavage of Safrrole (30) with MeONa and MeOH in Dipolar Aprotic Solvents (i) In HMPA: A mixture of **30** (162.0 mg, 1 mmol) and 13.5% MeONa–MeOH (1 ml) in HMPA (1.5 ml) was stirred at 150 °C for 2 h. The mixture was diluted with cold water (30 ml), and 10% NaOH (20 ml), then extracted with diethyl ether (30 ml $\times$ 2). The ether extract was purified by P-TLC (eluent CHCl_3) to give the starting material **30** (34.1 mg, 21.0%). The mother liquor was acidified (pH 5–6) with concentrated HCl and extracted with diethyl ether (40 ml $\times$ 3). The extract was washed with water, dried (MgSO_4), and evaporated. The residue was purified by P-TLC (eluent CHCl_3) to give an inseparable mixture (132.5 mg, 63.7%, yellow oil, *ca.* 1.0:1.5) of phenolic compounds (**34** and **35**), which were identified from the ^1H -NMR spectral data. IR ν_{max} cm^{-1} : 3430 (OH). ^1H -NMR (100 MHz, CDCl_3) δ : 1.88 (3H, d, $J=6.5$ Hz, CH=CHMe), 3.52 (3H, s, OCH_2OMe), 5.16, 5.18 (*ca.* 1.0:1.5, totally 2H, each s, OCH_2OMe), 6.08 (1H, m, CH=CHMe), 6.32 (1H, d, $J=15.5$ Hz, CH=CHMe), 6.77,

6.83 (totally 1H, each dd, $J=1.7, 8.1$ Hz, 6-H), 6.91, 6.98 (totally 1H, each d, $J=8.1$ Hz, 5-H), 6.95, 7.08 (totally 1H, each d, $J=1.7$ Hz, 2-H). High-resolution MS: Calcd for $C_{11}H_{14}O_3$: 194.0941. Found: 194.0929.

(ii) In DMSO: A mixture of **30** (162 mg, 1 mmol) and 13.5% MeONa–MeOH (1.5 ml) in DMSO (1.5 ml) was stirred at 150 °C for 2 h. Work-up of the mixture as described in (i) gave **30** (0.9 mg, 0.4%) and phenolic compounds (75.4 mg, 38.8%). The phenolic compounds were identified as an inseparable mixture (*ca.* 1.6:1.0) of **34** and **35** from the ^1H -NMR spectral data. IR ν_{max} cm^{-1} : 3425 (OH). ^1H -NMR (100 MHz, CDCl_3) δ : 1.83 (3H, d, $J=6.2$ Hz, CH=CHMe), 3.52 (3H, s, OCH_2OMe), 5.13, 5.15 (*ca.* 1.6:1.0, totally 2H, each s, OCH_2OMe), 6.05 (1H, m, CH=CHMe), 6.30 (1H, d, $J=14.5$ Hz, CH=CHMe), 6.75, 6.84 (totally 1H, each dd, $J=1.7, 8.0$ Hz, 6-H), 6.90, 6.98 (totally 1H, each d, $J=8.0$ Hz, 5-H), 6.96, 7.08 (totally 1H, each d, $J=1.7$ Hz, 2-H). High-resolution MS: Calcd for $C_{11}H_{14}O_3$: 194.0941. Found: 194.0945.

(iii) In MeOH: A mixture of **30** (162 mg, 1 mmol) and 13.5% MeONa–MeOH (2.5 ml) was stirred at 150 °C for 2 h. Work-up of the mixture as described in (i) gave **30** (126.4 mg, 77.1%) and phenolic compounds (1.3 mg, 0.7%).

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