Selective Syntheses Using Cyclodextrin as Catalyst. 1. Control of Orientation in the Attack of Dichlorocarbene at Phenolates

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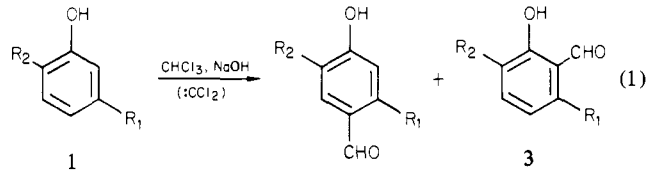
Abstract: 4-Hydroxybenzaldehydes, 2,4-dihydroxybenzaldehyde, and 4-(dichloromethyl)-2,5-cyclohexadienones were synthesized in virtually 100% selectivities and high yields from the corresponding phenols and chloroform in alkaline aqueous solutions by using α- or β-cyclodextrin (α- or β-CD) as catalyst. The regulation of the molar ratio of chloroform to CD below unity throughout the reaction time, by controlling the rate of addition of chloroform, was definitely required to attain high selectivity. Under these conditions, dichlorocarbene, prepared in situ from chloroform and sodium hydroxide, attacked overwhelmingly at the para carbon of phenols with almost perfect suppression of the reaction at the ortho carbon. The structure of the ternary molecular complex composed of β-CD, chloroform, and phenol, formed in the reaction mixture for the selective synthesis of 4-hydroxybenzaldehyde, was determined by NMR spectroscopy. The selective catalysis by CDs was attributed to the regulation of molecular conformation of phenols with respect to chloroform, and thus to dichlorocarbene, in the ternary molecular complex.

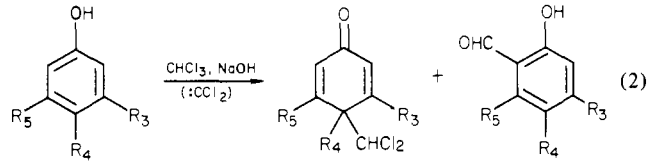
The attention to the catalyses by cyclodextrins (CDs), cyclic oligomers of 6–8 glucose units, has been rapidly increasing. One of the characteristics of the CD-catalyzed reactions is specificity, which is due to molecular complex formation of substrates with CDs prior to chemical transformation. Marked substrate specificities were reported for the catalyses by CDs in many bond cleavage reactions such as hydrolyses and decarboxylations.[1] In addition, the specificities in these reactions were controlled by covalent modification of CDs.[2,3] However, there have been only a few reports[4-9] on the product specificity exhibited by CDs, that is, specific catalyses by CDs in bond formation reactions.

In preliminary communications,[10] the authors reported that 4-hydroxybenzaldehyde, 2,4-dihydroxybenzaldehyde, 4-hydroxybenzoic acid, 2,5-cyclohexadienones, and 3-indolecarboxaldehyde are synthesized in high selectivities by use of CDs as catalyst. Furthermore, one-pot syntheses of chalcones and nitrovinylbenzoic acid were successfully achieved by using CDs.[11]

This paper describes the results of detailed analyses of the selective syntheses of 4-hydroxybenzaldehydes, 2,4-dihydroxybenzaldehyde, and 4-(dichloromethyl)-2,5-cyclohexadienones using CDs as catalyst. The selective catalyses by CDs involve the control of orientation in the attack of dichlorocarbene, prepared in situ from chloroform and sodium hydroxide, at phenols, as shown in eq 1 and 2. The dependence of the selectivities and yields on the structures of the phenols as well as on the methods of reactions will be shown. Kinetic studies will also be carried out. Furthermore, the structures of the molecular complexes of CDs with the reactants, formed in the reaction mixtures, will be determined by NMR spectroscopy. The reaction mechanism will be clarified on the basis of these results.



a, $R_1 = R_2 = H$
b, $R_1 = OH$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$
d, $R_1 = CH_3$; $R_2 = H$
e, $R_1 = C(CH_3)_3$; $R_2 = H$



a, $R_4 = CH_3$; $R_3 = R_5 = H$
b, $R_4 = C_6H_5$; $R_3 = R_5 = H$
c, $R_3 = R_4 = R_5 = CH_3$
d, R_4–R_5 = c-$(CH_2)_4$; $R_3 = H$

Experimental Section

Selective Syntheses Using CDs as Catalyst. The typical procedure was as follows. Phenol or its derivative, 1.0 g, and α- or β-cyclodextrin (α- or β-CD), 8.0 g, were dissolved in 50 mL of 10 wt % aqueous sodium hydroxide solution, to which chloroform was added dropwise with stirring at 60 °C. At 20-min intervals, the concentration of unreacted chloroform in the reaction mixture was determined by gas chromatography (Porapak Q column, 2 m, 170 °C). The rate of addition of chloroform to the mixture was controlled so that the molar ratio of chloroform to CD should be always smaller than unity. In the course of 8 h, 5 mL of chloroform was added. Then the reaction mixture was acidified with hydrochloric acid, followed by extraction with ethyl ether. The products, obtained as solid or liquid by evaporation of the ether layer, were analyzed by gas chromatography (Tenax GC column, 2 m, 300 °C).

Kinetics. To 10 wt % aqueous sodium hydroxide solution containing a phenol and α- or β-CD was added chloroform in 10 wt % aqueous sodium hydroxide solution at the beginning of the reaction. The initial concentrations of the phenol, CD, and chloroform, respectively were 2.0×10^{-1}, 3.0×10^{-2}, and 2.5×10^{-2} M. The formation of the products was followed by absorption spectroscopy.[12] The concentration of unreacted chloroform in the reaction mixture was determined at 20-min intervals by gas chromatography.

Determination of the Structures of Molecular Complexes in the Reaction Mixture by NMR Spectroscopy. The time-averaged position of phenol (**1a**) in the cavity of β-CD in alkaline aqueous solution with or without chloroform was determined by the ^1H NMR method described in detail previously.[13-15] The position of **1a**, in which the theoretical

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Table I. Yields and Selectivities for the Reactions between Various Phenols and Chloroform in the Presence and the Absence of CDs as Catalyst

phenols	CD used	product and its yield, mol %[a] para attack	ortho attack	selectivity for para attack, %
1a	β-CD	2a, 65 (92)	3a, 0 (0)	100
	α-CD	62 (72)	10 (12)	86
	none	18 (25)	35 (49)	34
1b	β-CD	2b, 96 (97)	3b, 0 (0)	100
	none	24 (31)	40 (52)	38
1c	β-CD	2c, 11 (85)	3c, 0 (0)	100
	α-CD	12 (78)	2 (13)	86
	none	28 (38)	18 (24)	61
1d	β-CD	2d, 15 (52)	3d, 8 (28)	65
	none	31 (47)	26 (39)	54
1e	β-CD	2e, 16 (41)	3e, 16 (41)	50
	none	15 (40)	16 (43)	48
4a	β-CD	5a, 65 (89)	6a, 2 (3)	97
	none	8 (25)	20 (63)	29
4b	β-CD	5b, 75 (90)	6b, 3 (4)	96
	none	6 (9)	44 (66)	12
4c	β-CD	5c, 82 (93)	6c, 0 (0)	100
	none	5 (11)	28 (62)	15
4d	β-CD	5d, 56 (88)	6d, 0 (0)	100
	α-CD	38 (81)	3 (6)	93
	none	10 (18)	43 (77)	19

[a] The numbers in parentheses are the values calculated in consideration of recovered phenols.

magnitudes (Δ_{calcd}'s) of the anisotropic shielding effects of its aromatic ring on the various protons of β-CD were in best agreement with the experimentally determined ^1H chemical shift changes (Δ_{obsd}'s), was taken as the time-averaged position. ^1H NMR spectra were measured in D_2O at 25 °C by a JEOL PS-100 spectrometer, and Δ_{obsd}'s were determined as the limiting values with respect to the concentrations of **1a** and chloroform.

^{13}C NMR spectra were taken at 25 °C on a JEOL PFT-100 spectrometer operating at 25.03 MHz, connected with JEOL EC-100 computer.

Results

Selective Syntheses of 4-Hydroxybenzaldehydes and 4-(Dichloromethyl)-2,5-cyclohexadienones Using CDs as Catalyst. Table I shows the results for the reactions of various phenols with chloroform in alkaline aqueous solutions with or without CD.

For para-unsubstituted phenols **1a–c**, the products **2a–c** due to the introduction of formyl groups at the para positions with respect to the hydroxyl groups are produced in 100% selectivities in the presence of β-CD. Selective syntheses are also achieved by use of α-CD, although the selectivities are slightly lower than those in the reactions using β-CD. These products are formed by the selective attack of dichlorocarbene at the para position of phenol or its derivatives, followed by the hydrolyses of C–Cl bonds.[16] The amount of product resulting from introduction of a formyl group at the ortho position is minimal, which contrasts markedly to the production of large amounts of **3a–c** in the absence of CD (see eq 1).

As clearly seen from the results for **1d–e**, the alkyl substituents at the meta positions of para-unsubstituted phenols largely decrease the selectivity for the production of 4-hydroxybenzaldehydes. This result shows the importance of the stereochemistry of inclusion complexes in the selective reactions.

4-(Dichloromethyl)-2,5-cyclohexadienones **5a–d** are also successfully synthesized in virtually 100% selectivities and high yields with CDs as catalyst. In their absence, however, the productions of the ortho-formylated compounds **6a–d** are predominant, and the selectivities and yields for **5a–d** are only 12–29% and 5–10 mol %, respectively (see eq 2).

Effect of Molar Ratio of β-CD to Chloroform on Selectivities. Figure 1 depicts the selectivity of the production of **2a** from **1a** or **5a** from **4a** as a function of the initial molar ratio of β-CD to **1a** or **4a**. By the dropwise method, in which chloroform is added dropwise while the molar ratio of chloroform to β-CD is maintained at unity or smaller as described in the Experimental Section, the selectivity is almost 100% in a wide range of the ratio of β-CD to **1a** or **4a**. Thus, selective syntheses using small amount of β-CD are achieved by this method.

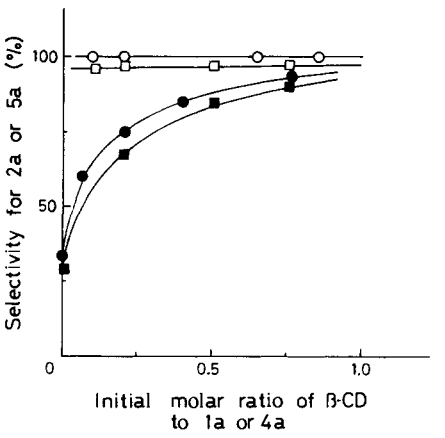

Figure 1. Dependence of the selectivity of the formation of **2a** or **5a** on the initial molar ratio of β-CD to **1a** or **4a** for two reaction methods: (○) dropwise method for **2a**; (●) all at once method for **2a**; (□) dropwise method for **5a**; (■) all at once method for **5a**. The details for these two methods are described in text.

On the other hand, when all the chloroform is added at the beginning of the reaction (all at once method), the selectivity of the formation of **2a** or **5a** rapidly decreases with the decrease in the ratio. A similar trend was reported by Ohara and Fukuda.[9] Thus, the initial molar ratio of β-CD to **1a** or **4a** has to be larger than about 0.6 to attain the selectivity of 90% or so.

These results indicate that the molecular complex formation between β-CD and chloroform, rather than that between β-CD and phenols, has a predominant role in the present selective syntheses.

Kinetics. Table II shows the results of kinetic studies on the selective syntheses using CDs as catalyst. The rates of consumption of chloroform in the presence of α-CD and β-CD are about 1.4- and 1.9-fold slower than that in their absence. In addition, the rates are rather independent of the phenols used, indicating protection of chloroform by CDs from hydrolyses even in the presence of considerable amounts of phenols.

For **1a** and **1c**, the molar fraction (f_o) of chloroform incorporated into the ortho position of phenols with respect to the amount of chloroform consumed is zero in the presence of β-CD. On the other hand, the corresponding value (f_p) for the para position of phenols in its presence are almost identical with (for **1a**) or 3-fold smaller than (for **1c**) the values in its absence. Thus, highly selective syntheses of **2a** and **2c** using β-CD are attributed to the inhibition of the reaction at the ortho position rather than the acceleration of the rection at the para position.

The f_o's for **1a** and **1c** in the presence of α-CD are not zero but still are considerably smaller than that in its absence. In addition, the f_p for **1a** in its presence is 1.6-fold larger than that in its absence, whereas the f_p for **1c** is suppressed by α-CD only by 13%. As a result, the reaction at the para position is promoted by α-CD, compared with the reaction at the ortho position.

The poor selectivity for the reaction of **1d** is due to suppression of f_o and f_p by CDs in almost identical magnitudes. For **1e**, neither α-CD nor β-CD shows considerable effects on f_p and f_o.

The selectivities for the para attack, determined from f_p and f_o, agree fairly well with the values in Table I determined by product analyses.

Structures of Molecular Complexes Formed in the Reaction Mixture for Selective Synthesis. **7** in Figure 2 depicts the structure of the molecular complex between **1a** and β-CD in 10 wt % aqueous sodium hydroxide solution, determined by NMR spectroscopy. **1a** penetrates the cavity of β-CD from the side involving the para carbon atom. The center of the aromatic ring is located at the height of +1.0 Å with respect to the plane comprised of

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Table II. Rates and Selectivities for the Attack of Dichlorocarbene at Various Phenols in the Presence and Absence of CDs[a,b]

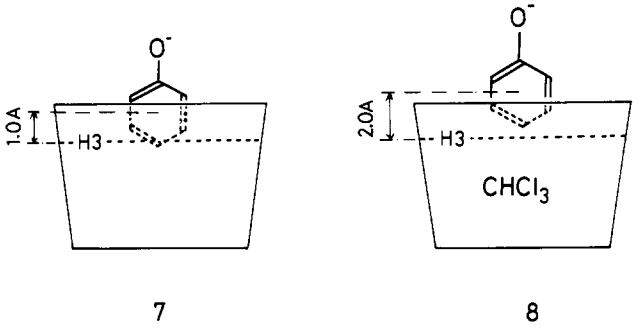
phenols	consumption of chloroform for 1 h, %		f_p[c]		f_o[c]		selectivity for para attack, %	
	with CD	without CD	with CD	without CD	with CD	without CD	with CD	without CD
1a	12	24	0.17	0.13	0.000	0.19	100	41
	17		0.21		0.031		87	
1c	12	24	0.019	0.063	0.000	0.031	100	67
	17		0.055		0.014		80	
1d	13	23	0.032	0.11	0.016	0.090	67	55
	16		0.071		0.046		61	
1e	13	23	0.024	0.024	0.025	0.025	49	49
	17		0.026		0.026		50	

[a] The reaction conditions are shown in the Experimental Section. [b] The upper and lower numbers refer to β-CD and α-CD, respectively. [c] f_p and f_o are the molar fractions of chloroform incorporated into the para and ortho positions of phenols, respectively, with respect to the total amount of chloroform consumed.

Table III. Calculated and Observed Changes in the ^{1}H Chemical Shifts of β-CD for the Molecular Complex Formations[a]

molecular complex	protons of β-CD	Δ_{calcd},[b] ppm	Δ_{obsd},[b] ppm
β-CD–1a	H-3	+0.14	+0.15
	H-5	−0.03	−0.05
β-CD–1a–$CHCl_3$	H-3	+0.07	+0.07
	H-5	−0.05	−0.07

[a] In 10 wt % aqueous sodium hydroxide solution at 25 °C. [b] Positive values refer to increase in the shielding.



7 8

Figure 2. Time-averaged conformation of the molecular complex **7** formed from β-CD and **1a**, and that of the ternary molecular complex **8** formed from β-CD, **1a**, and chloroform in alkaline aqueous solution; -----H3----- shows the plane comprised of seven H-3 atoms of β-CD.

seven H-3 atoms of β-CD. The positive sign in height refers to the side of the secondary hydroxyl groups.

In alkaline solution containing β-CD, **1a**, and chloroform, the ternary molecular complex **8** is also formed. Here, the cavity is largely occupied by chloroform. The penetration of **1a** in the cavity is considerably shallower than that in **7** without chloroform, as clearly shown by the height (+2.0 Å) of the center of the aromatic ring.

As shown in Table III, the Δ_{obsd}'s for both H-3 and H-5 atoms of β-CD are in satisfactory agreement with the corresponding Δ_{calcd}'s.

The direction of penetration of **1a** was determined by ^{13}C NMR spectroscopy. On formation of the molecular complex **7**, the signals for the ortho, meta, and para carbons of **1a** shifted toward lower magnetic field by −0.4, −0.1, and +0.3 ppm. Thus, the penetration depths are in the order para > meta > ortho, since the larger magnitude of the shift toward lower magnetic field corresponds to deeper penetration.[15]

The formation of **8** is further confirmed by the fact that the ^{1}H chemical shift of chloroform is shifted toward lower magnetic field by 0.14 ppm, which is due to the anisotropic shielding effect by the aromatic ring of **1a**.

Discussion

Reaction Mechanism of Selective Syntheses Using β-CD as Catalyst. The mechanism of the selective catalyses by β-CD is proposed as depicted in Figure 3, on the basis of the result of the present NMR study of the molecular complexes in the reaction mixtures.

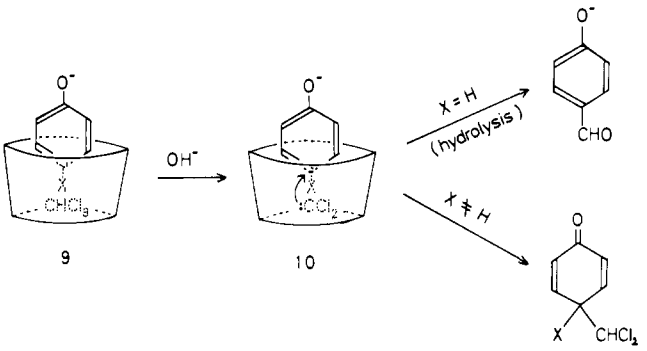
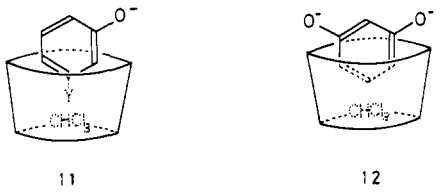


Figure 3. Reaction mechanism of selective syntheses of **2a**, **2c**, and **5a–d** using β-CD as catalyst: X = H (for **2a** and **2c**) and alkyl or aryl (for **5a–d**).

First, a ternary molecular complex **9** is formed from β-CD, chloroform, and phenol or its derivative, in which the cavity of β-CD is largely occupied by chloroform. Phenol or its derivative in its anionic form penetrates shallowly in the cavity from the side involving the para carbon atom, since the inclusion of this apolar side in the apolar cavity is more favorable than the inclusion of the polar side involving the phenoxide oxygen atom. Dichlorocarbene, formed in the cavity by the reaction of chloroform with hydroxide ion, should attack overwhelmingly at the para carbon atom of phenol located in close proximity, as shown in Figure 3 (**10**). The attack at the ortho carbon atom of phenol is sterically much more unfavorable. Thus, the selective catalyses by β-CD in the para reactions for various phenols are due to the regulation of the molecular conformation of phenols with respect to chloroform in the ternary molecular complex.

The formation of the ternary molecular complex in the initial state is not necessarily required for selective reactions. Instead, the regulation of the molecular conformation can be also accomplished by the favorable interaction between the apolar cavity and the apolar side of the phenol only in the transition state. The resulting products are free from complexation with β-CD. This can be associated with selective reactions involving highly bulky phenols such as **4b–d**.

The proposed mechanism is supported by the fact that the selectivity for the formulation of **2a** or **5a** is largely dependent on the methods of addition of chloroform (Figure 1). In the dropwise method, where the molar ratio of chloroform to β-CD is always kept below unity, most of the chloroform in the reaction mixture forms complexes with β-CD. The reaction proceeds predominantly in the mechanism shown in Figure 3, resulting in high selectivity. In the all at once method, however, a considerable amount of chloroform is free from complexation with β-CD, since chloroform is present in large excess of β-CD. Thus, the reaction involving free chloroform, which exhibits low selectivity, takes place competitively with the reaction depicted in Figure 3. Alternatively, chloroform present in large excess can prevent the regulation of



11 12

Figure 4. Ternary molecular complex composed of β-CD, chloroform, and **1d** or **1e** (**11**) and that composed of β-CD, chloroform, and **1b** (**12**). Y = CH_3 (for **1d**) and $C(CH_3)_3$ (for **1e**).

the molecular conformation between chloroform and the phenol by β-CD due to competition with the phenol in binding with β-CD.

Comparison of Catalytic Activities of α-CD and β-CD. The lower selectivity in the reaction using α-CD than that in the reaction using β-CD comes from weaker regulation of the molecular conformation of phenol or its derivative with respect to chloroform in the ternary molecular complex. The penetration of phenols in the cavity of α-CD is shallower than that in the cavity of β-CD. For example, the center of the aromatic ring of **1a** is located at the height of +2.0 Å from the plane comprised of seven H-3 atoms in the ternary molecular complex **8** of β-CD. In the ternary molecular complex composed of α-CD, chloroform, and **1a**, however, the height is larger than +3.5 Å since no chemical shift changes were observed for either α-CD or **1a**.[17] In the selective catalyses by α-CD, the transition state should involve the ternary molecular complex composed of α-CD, phenol, and dichlorocarbene.

The above argument is consistent with the larger f_p value for the reaction using α-CD than that in the reaction using β-CD. The increase of the activation energy due to the requirement for the change of the molecular conformation of dichlorocarbene and phenols in the cavity, a sterically restricted reaction field, prior to the transformation should be smaller for α-CD showing shallower penetration.

Effects of Meta Substituents of Phenols on Selective Catalyses by CDs. The structures of the ternary molecular complexes, formed in the reaction between chloroform with phenols possessing substituents at the meta position of the hydroxyl group, are shown in Figure 4. In the ternary molecular complex **11** for **1d** or **1e**, phenols penetrate the cavity from the side involving the apolar substituents at the meta position. The low selectivity of the reaction at the para position for these phenols is attributable to smallness of geometric discrimination between the para and the ortho carbon atoms in the acttack of dichlorocarbene.

In the reaction of a symmetrically substituted phenol, **4c**, which possesses the alkyl groups at the 3, 4, and 5 positions, **4c** probably penetrates in the cavity from the side involving the methyl group at the 4 position rather than from the side involving the methyl group at the 3 or 5 position, resulting in a selective reaction at the 4 position.

In the case of **1b**, the polar property of the phenoxide ion at the meta position requires the inclusion of the part of the aromatic ring involving the C-5 atom in the cavity, as shown in **12**. Thus, dichlorocarbene predominantly attacks at the C-4 or C-6 atom without the attack at the C-2 atom, producing **2b** in 100% selectivity.

These arguments are consistent with the importance of geometry of inclusion complexes in the CD-accelerated cleavages of esters.[1,14,18]

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Registry No. **1a**, 108-95-2; **1b**, 108-46-3; **1c**, 95-48-7; **1d**, 108-39-4; **1e**, 585-34-2; **2a**, 123-08-0; **2b**, 95-01-2; **2c**, 15174-69-3; **2d**, 41438-18-0; **2e**, 84694-00-8; **4a**, 106-44-5; **46**, 92-69-3; **4c**, 527-54-8; **4d**, 1125-78-6; **5a**, 6611-78-5; **5b**, 78227-72-2; **5c**, 5682-84-8; **5d**, 84694-01-9; α-CD, 10016-20-3; β-CD, 7585-39-9; dichlorocarbene, 1605-72-7; β-CD-**1a**, 84694-02-0; β-CD-**1a**-$CHCl_3$, 84694-03-1.

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Short Syntheses of Furan and Catechol Derivatives. A Synthesis of Hydrourushiol[1,2]

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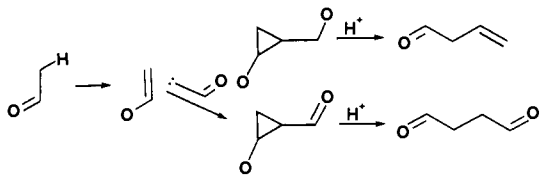
Abstract: The copper-catalyzed decomposition of ethyl diazopyruvate in enol ethers is shown to yield alkoxydihydrofuroates, whose exposure to acid leads to ethyl α-furoates. The latter are also the products of the copper-induced interaction of ethyl diazopyruvate with acetylenes. The conversion of one furoate into a furan and another into a furanoid terpene system is described. The Fétizon oxidation of primary β-alkoxycyclopropylcarbinols is shown to give alkoxydihydrofurans. The formation of a masked, 1,2,5-triketo system by the copper-assisted decomposition of 1-diazo-3,3-dimethoxy-2-butanone in *n*-butyl vinyl ether and subsequent acid-catalyzed unraveling of the resultant β-alkoxycyclopropyl ketone are portrayed. Ring scission of the intermediate in methanolic acid at elevated temperature yields veratrole. Utilization of this new method of synthesis of aromatic compounds of the catechol type in the synthesis of hydrourushiol is illustrated.

The reaction sequences depicted in eq 1 have served for some



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time as the basis of a general procedure for the preparation of γ-difunctionalized organic substances and their use in natural product synthesis.[7] The most vital step in this general method

(1) Based on work described first in the Ph.D. Dissertations of B. L. Buckwalter and M. E. Alonso, Indiana University, 1973 and 1974, respectively.

(2) The work was presented by E.W. in a plenary lecture at the Sixième Colloque de Chimie Heterocyclique, Mulhouse, France, July 1-3, 1980. Wenkert, E. *Heterocycles* **1980**, *14*, 1703.

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