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TETRAHEDRON REPORT NUMBER 420

Regio- and Stereoselective Synthesis of γ-Alkylidenebutenolides and Related Compounds

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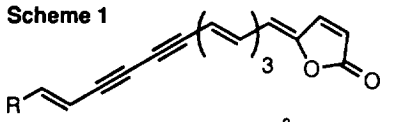
INTRODUCTION

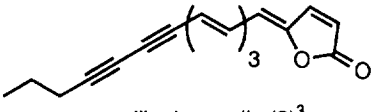
Butenolides[1,2] represent a large number of natural products and their analogues of medicinal and biological interest, such as steroidal cardenolides. Over the past few decades, an increasing number of stereodefined γ-

alkylidenebutenolides have been isolated from natural sources, and many of them have been shown to display a wide range of biological activities, such as (i) inhibition of cholesterol biosynthesis observed with xerulin (**1a**), xerulinic acid (**1b**), and dihydroxerulin (**2**),[3] (ii) cytotoxicity observed with goniobutenolides A (**3a**) and B (**3b**)[4-10] and nostoclides (**4**),[11,12] and (iii) antibiotic activity observed with rubrolides (**5**)[13,14] and tetrenolin (**6**).[15] These and some other representative γ-alkylidenebutenolides[3-38] are shown in Scheme 1.

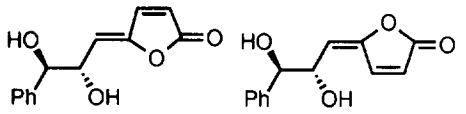
Scheme 1



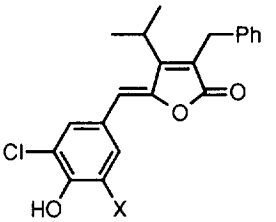
xerulin (**1a**: R = Me)[3]
xerulinic acid (**1b**: R = COOH)[3]



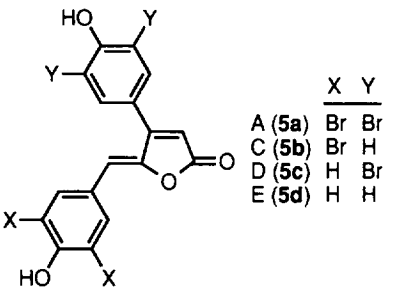
dihydroxerulin (**2**)[3]



goniobutenolide A (**3a**) and B (**3b**)[4-10]

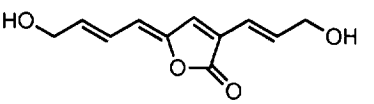


nostoclide I (**4a**: X = Cl) and II (**4b**: X = H)[11,12]

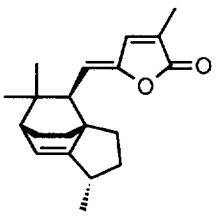


	X	Y
A (**5a**)	Br	Br
C (**5b**)	Br	H
D (**5c**)	H	Br
E (**5d**)	H	H

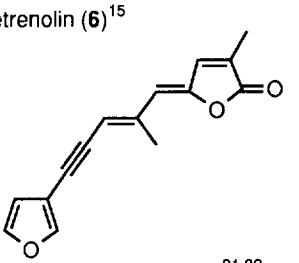
rubrolides (**5**)[13,14]



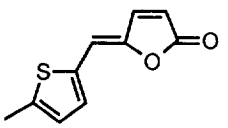
tetrenolin (**6**)[15]



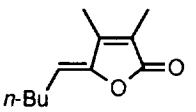
eremolactone (**7**)[16-20]



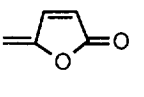
freelingyne (**8**)[21,22]



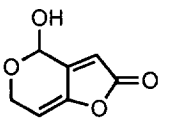
thiophenbutenolide (**9**)[23,24]



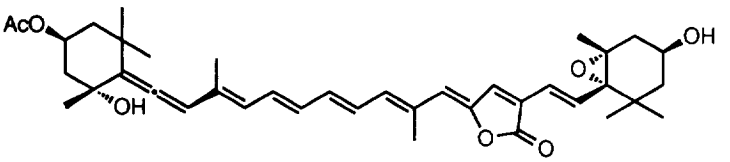
bovolide (**10**)[25-27]



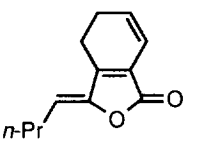
protoanemonin (**11**)[28-30]



patulin (**12**)[31,32]



peridinin (**13**)[33-36]



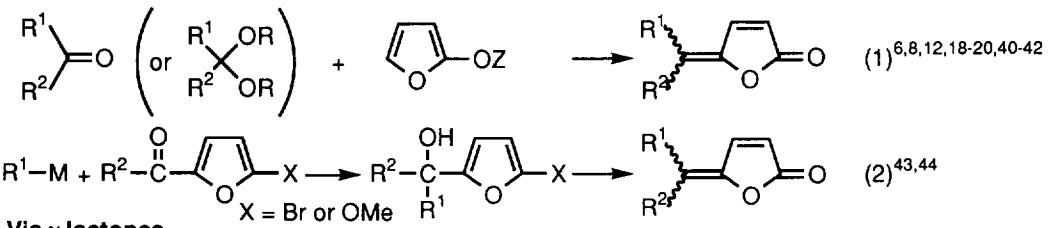
ligustilide (**14**)[37,38]

This review is primarily concerned about efficient and selective syntheses of γ-alkylidenebutenolides and related compounds. It should be noted that the majority of the compounds shown in Scheme 1 contain a (*Z*)-γ-alkylidene moiety, and it does appear that, for steric and electronic reasons, the *Z* isomers are, in general, thermodynamically favored. And yet, most of the synthetic methods developed earlier produce *E* and *Z* mixtures. Moreover, steps generating the γ-alkylidene moiety often occur late in the synthetic schemes, rendering such syntheses rather unattractive. Mainly during the past ten or dozen years, several organometallic methods, some of which are highly selective, have been reported. In particular, palladium-catalyzed lactonization of alkynoic acids appears to be highly promising. It also provides procedures that are applicable to the stereoselective synthesis of either *Z* or *E* stereoisomers. The main objective of this review is to present a current overview of these efficient and selective organometallic methods. Earlier methods were reviewed comprehensively by Rao[1,2] through the middle of 1976. However, those that are pertinent to the discussion presented herein are briefly reviewed again to update the literature information along this line and to provide a proper perspective on the entitled topic.

NONSTEREOSELECTIVE SYNTHESES VIA ALKYLIDENATION OF FIVE-MEMBERED HETEROCYCLES

Scheme 2

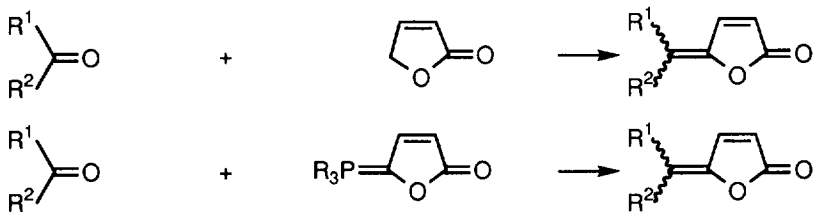
Via 2-oxyfurans



(1)[6,8,12,18-20,40-42]

(2)[43,44]

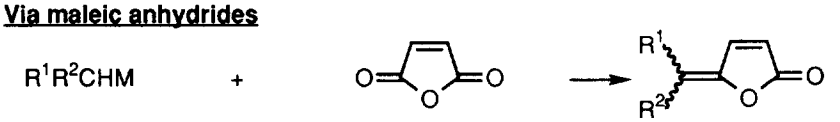
Via γ-lactones



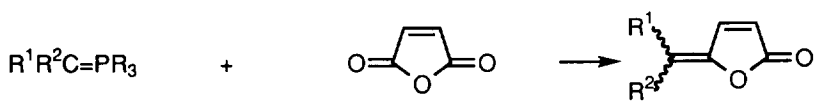
(3)[23,45-48]

(4)[22,49,50]

Via maleic anhydrides

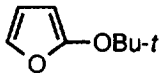
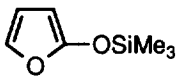
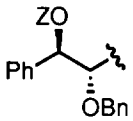
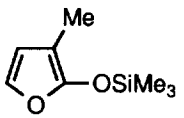
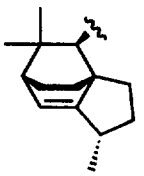
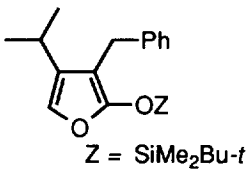
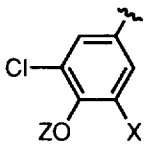
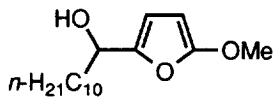


R^1R^2CHM + (5)[25]



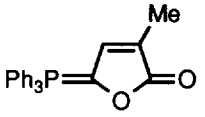
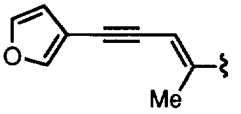
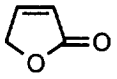
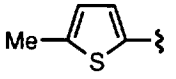
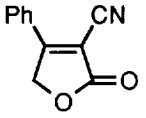
$R^1R^2C{=}PR_3$ + (6)[51-56]

Table 1. Synthesis of γ-Alkylidenebutenolides via 2-Oxyfurans

2-Oxyfuran	R^1 of R^1CHO	Method[a]	R	Y	Yield(%)	*Z/E*	Ref.
	Ph	**A**	H	H	61	*b*	40
	n-Pr	**A**	H	H	45	*b*	40
	Ph	**B**	H	H	91	50/50	42
	n-Pent	**B**	H	H	94	50/50	42
	2-Thienyl	**B**	H	H	91	67/33	42
	n-PrC≡C-	**B**	H	H	92	67/33	42
		**C**	**3a + 3b**[e]		93	94/6	7,8,41
		**D**	**7**[e]		88	67/33	18
		E	**7**[e]		36	50/50	19
		**F**	**4**[e]		≥90	100/0	12
	*c*	**G**	H	H	65	NA[d]	44

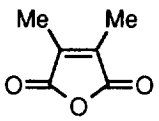
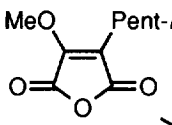
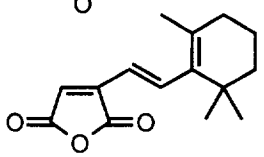
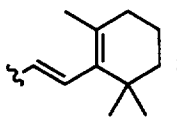
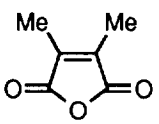
[a] **A**: 1. *t*-BuLi, 2. *p*-TsOH. **B**: Ac_2O, NEt_3, 4-pyrrolidinopyridine. **C**: 1. $Cl_2Ti(i\text{-}OPr)_2$, 2. MsCl, NEt_3, 3. $i\text{-}Pr_2NEt$. **D**: 1. $SnCl_4$, 2. Bu_4NF, 3. MsCl, 4. NEt_3. **E**: 1. $SnCl_4$, 2. NEt_3, TFAA. **F**: 1. $t\text{-}BuMe_2SiOTf$, 2. DBU, 3. HCl. **G**: $ZnCl_2$. [b] The formation of one stereoisomer is reported, but no detailed information is available. [c] Not applicable. The oxyfuran was prepared from *n*-decylmagnesium bromide and 5-bromofurfural. [d] NA - not available. [e] See Scheme 1 for their structures.

Table 2. Synthesis of γ-Alkylidenebutenolides via γ-Lactones

γ-Lactone	R^1 of R^1CHO	Conditions[a]	Product[b] R	Y	Yield(%)	Z/E	Ref.
	*p*-$NO_2C_6H_4$-	**A**	H	Me	24	NA[c]	49,50
	p-$MeOC_6H_4$-	**A**	H	Me	30	NA[c]	49,50
		**B**	**8**[d]		65	60/40	22
		**C**	**9**[d]		65	NA[c]	23
	Ph	**C**	Ph	CN	82	NA[c]	47,48
	Me_2N	**D**	Ph	CN	87	NA[c]	47,48

[a] **A**: CH_2Cl_2, reflux. **B**: DMSO. **C**: piperidine, AcOH, reflux. **D**: $POCl_3$, DMF. [b] See Table 1 for this structure. [c] NA - not available. [d] See Scheme 1 for the structure.

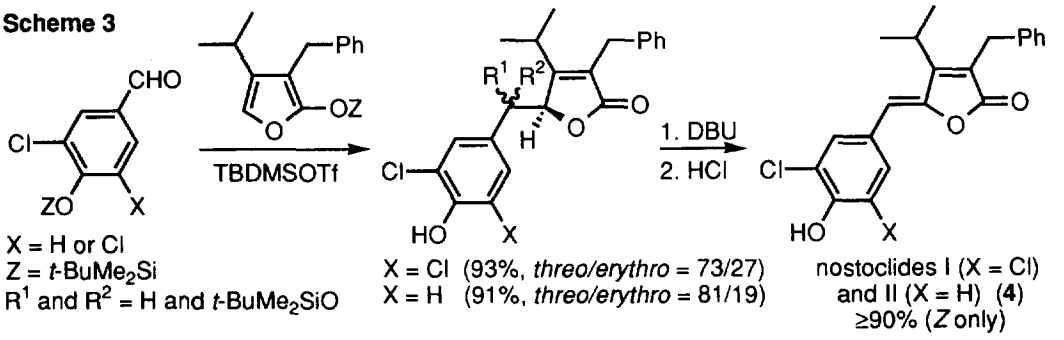
Table 3. Synthesis of γ-Alkylidenebutenolides via Maleic Anhydride Derivatives

Maleic anhydride	Reagent	Conditions[a]	Product[b] R^1	R	Y	Yield(%)	Z/E	Ref.
	$Ph_3P{=}CHR^1$	**A**	COOMe	Me	Me	98	62/38	51,56
	$Ph_3P{=}CHR^1$	**A**	COMe	Me	Me	76	68/32	51,56
	$Ph_3P{=}CHR^1$	NA[c]	COOMe	MeO	*n*-Pent	NA[c]	75/25	52
	$Ph_3P{=}CHR^1$	**B**	COMe	H 		35	29/71	53-55
	R^1CH_2MgBr	**C**	*n*-Bu	**10**[d]		75	NA[c]	25
	R^1CH_2MgBr	**C**	Ph	Me	Me	NA[c]	NA[c]	25
	R^1CH_2MgBr	**C**	*c*-C_6H_{11}	Me	Me	NA[c]	NA[c]	25

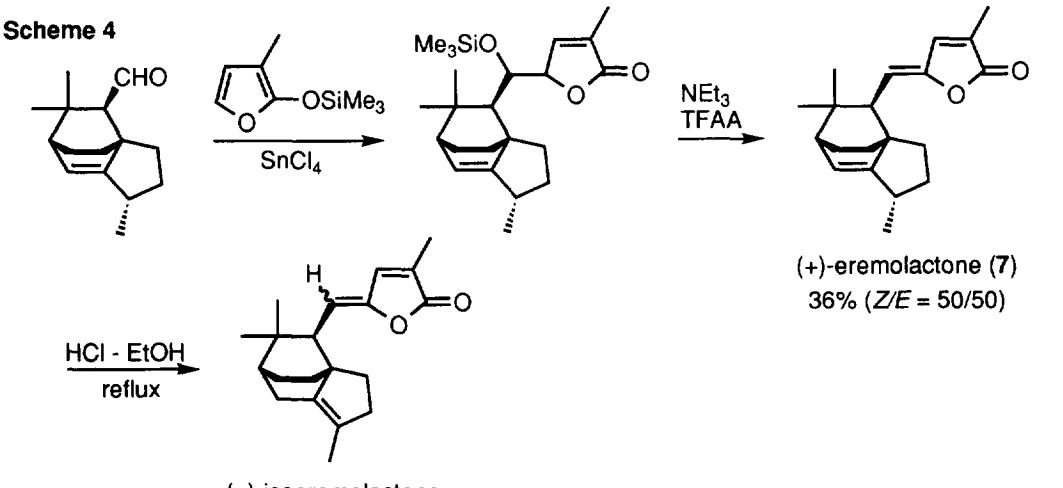
[a] **A**: $CHCl_3$, reflux. **B**: benzene, reflux. **C**: 1. -70°C, 2. $KHSO_4$. [b] See Table 1 for this structure. [c] NA - not available. [d] See Scheme 1 for the structure.

One of the most widely employed strategies[39] is alkylidenation of preformed five-membered oxygen-containing heterocycles, such as 2-oxyfurans,[6,8,12,18-20,40-44] γ-lactones,[22,23,45-50] *i.e.*, butenolides and butanolides, and maleic anhydrides[25,51-56] (Scheme 2). Oxyfurans and γ-lactones have been used mainly as nucleophiles, while maleic anhydrides have served as electrophiles. A number of natural products containing a stereodefined alkylidene moiety have been synthesized using this synthetic strategy. Some representative examples of the synthesis of γ-alkylidenebutenolides are shown in Tables 1-3. As such, these alkylidenation reactions are nonstereoselective, producing mixtures of the *E* and *Z* isomers in the absence of any overriding factors favoring one or the other. This can severely limit the product yields and present separation problems which can be difficult. Particularly damaging is the fact that the alkylidenation step generally occurs at a late stage of synthesis, often in the last step. Some specific examples of alkylidenation reactions leading to the syntheses of natural products are highlighted in Schemes 3-6.

Scheme 3

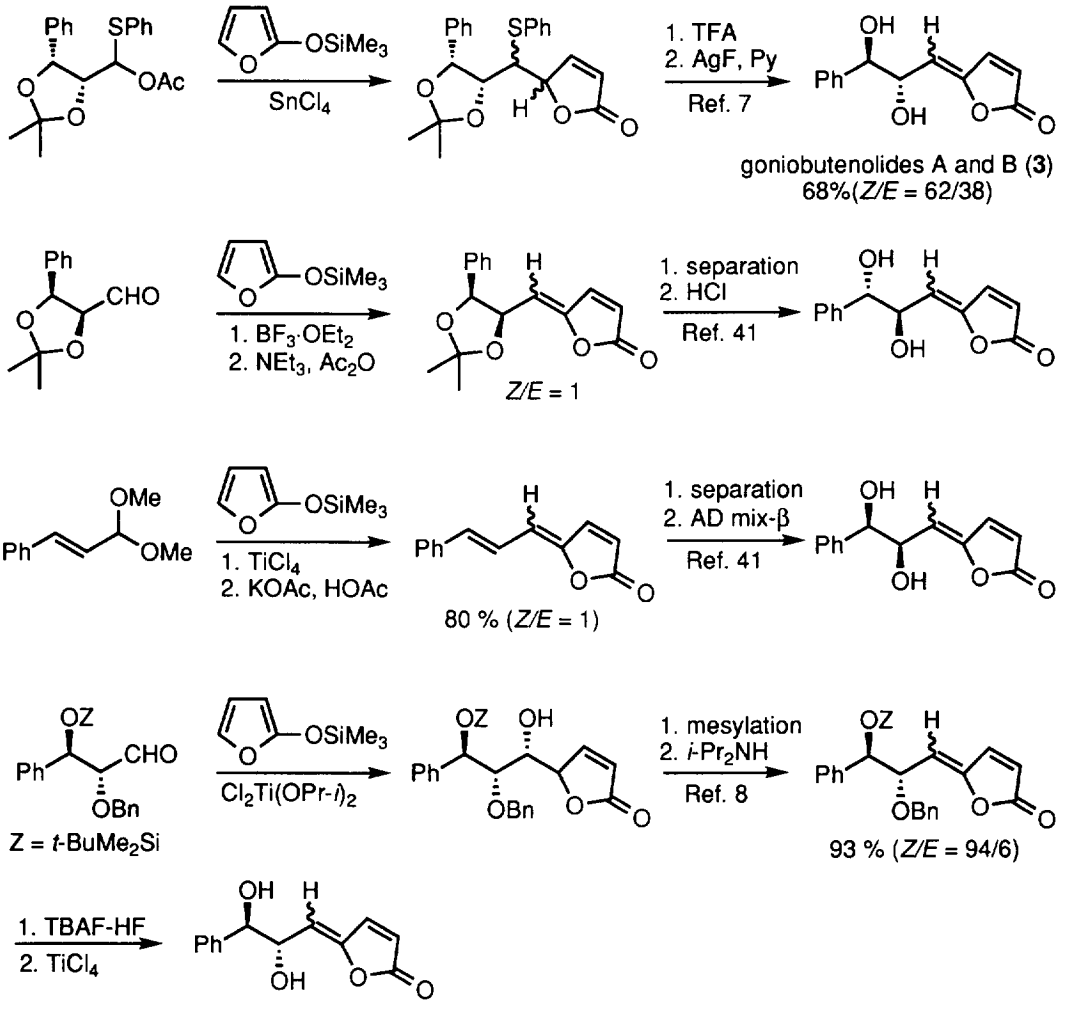


Scheme 4



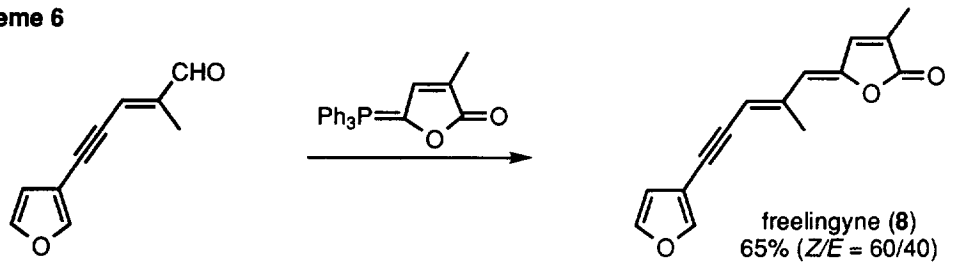
In the synthesis of nostoclides I and II,[12] shown in Scheme 3, TBDMSOTf-induced aldolization leads to 2.7/1 to 4.3/1 diastereomeric mixtures of the penultimate products in >90% yields. In this sense, diastereo-control in the reaction is at best modest. Thus, the exclusive formation of the desired *Z* isomers of nostoclides I and II must be attributable to the presumed strong kinetic and/or thermodynamic preferance for the formation of the *Z* isomer due to the presence of an isopropyl group in the ß position. In accord with this interpretation, most of the other syntheses employing this strategy, such as those of eremolactone (**7**)[19,18] and goniobutenolides (**3**)[7,41] resulted in low *Z*/*E* ratios (Schemes 4 and 5). However, more recent results indicate that the diastereoselectivity can be improved through appropriate modifications of reaction conditions.[8]

Scheme 5



In the synthesis of freelingyne (**8**),[22] the final alkylidenation step gives a 60/40 mixture of the *Z* and *E* isomers in 65% combined yield (Scheme 6).

Scheme 6

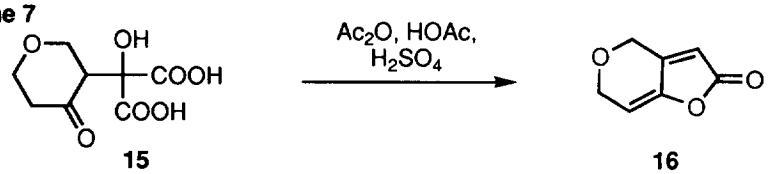


NONSTEREOSELECTIVE SYNTHESES VIA γ-KETOACIDS AND γ-HYDROXYACIDS

1. Via γ-Ketoacids

Lactonization of γ-ketoacids and γ-hydroxyacids is one of the oldest routes to γ-alkylidenebutenolides. Conversion of γ-oxo-2-pentenoic acid into protoanemonin (**11**) in 30% yield[29,30] and that of a ketol **15** into desoxypatulin (**16**)[31] in an unspecified yield as shown in Scheme 7 represent some of the earliest examples. Several additional examples are summarized in Table 4.

Scheme 7



15 **16**

Scheme 8

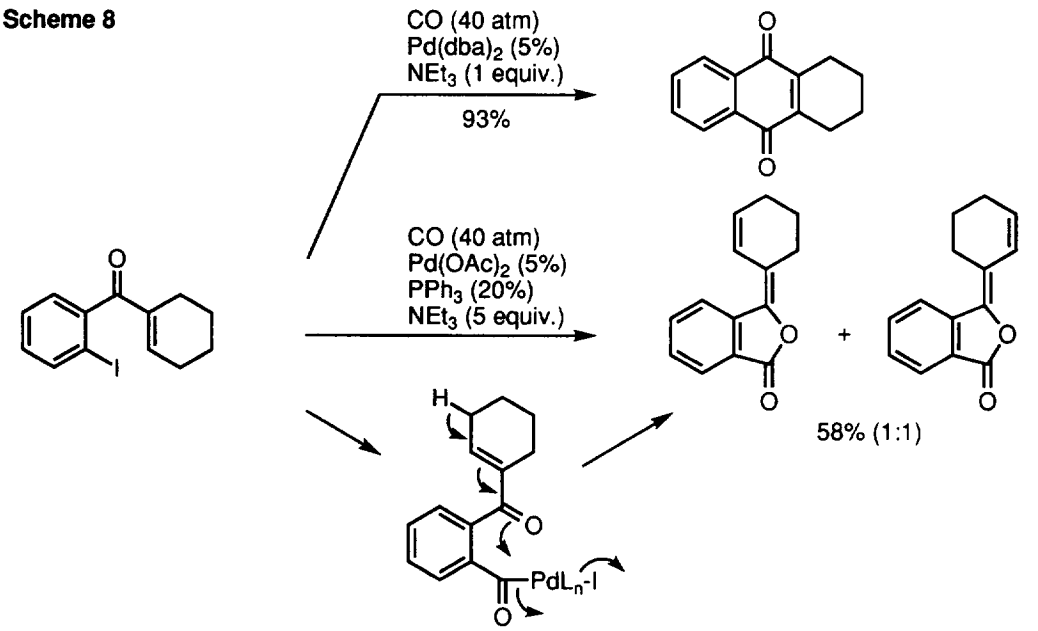
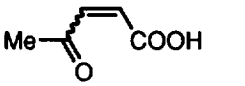
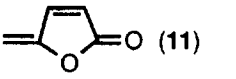
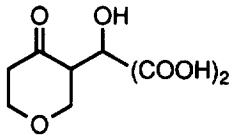
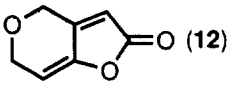
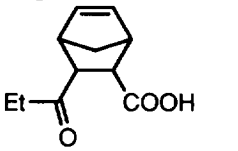
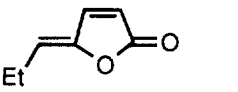
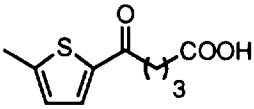
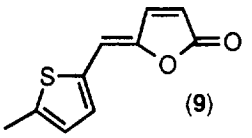
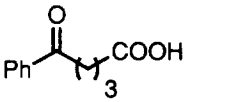
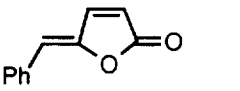
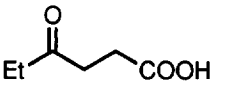
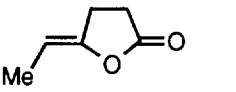
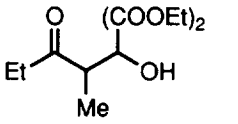
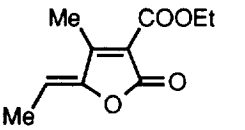
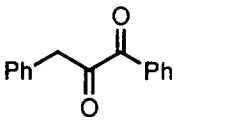
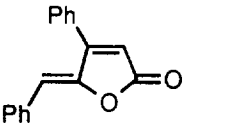
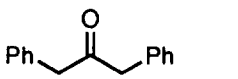
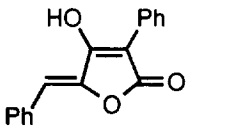


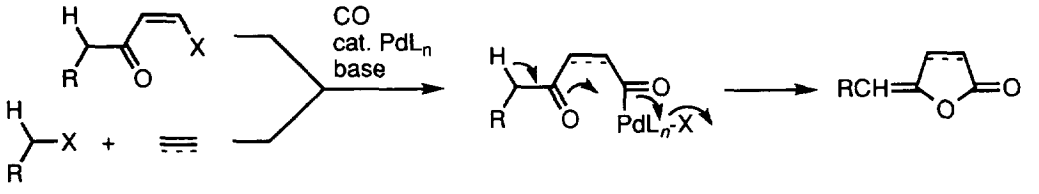
Table 4. Synthesis of γ-Alkylidenebutenolides via Ketoacids or Other Carbonyl Compounds without the Use of Transition Metal Complexes

Carbonyl Compound	Conditions[a]	Product	Yield(%)	*Z/E*	Ref.
	**A**	 **(11)**	30	NA[b]	29
	**B**	 **(12)**	2	*E* only	31,32
	**C**		63	NA[b]	57
	**D**	 **(9)**	38	92/8	58
	**D**		65	NA[b]	24,58
	**E**		40	NA[b]	59
	**F**		23	NA[b]	60
	**G**		60	NA[b]	61-63
	**H**		35	NA[b]	64

[a] **A**: Ac_2O-HOAc-H_2SO_4. **B**: 1. Δ, Ac_2O-HOAc, 2. Ac_2O-HOAc-H_2SO_4, 3. NBS, Bz_2O_2, 4. AgOAc, 5. Ac_2O-HOAc-H_2SO_4. **C**: 1. Ac_2O-HCl, 2. Δ, retro Diels-Alder. **D**: 1. Br_2, *p*-TsOH or NaOAc, Ac_2O. **E**: *p*-TsOH. **F**: P_2O_5-$MeSO_3H$. **G**: $Ph_3P{=}C{=}C(OEt)_2$. **H**: 1. $(COOEt)_2$, NaOEt, 2. Δ. [b] NA - not available.

A new and potentially general route to γ-alkylidenebutenolides and -butanolides via γ-ketoacylpalladium complexes was accidentally discovered by us in 1986[65] (Scheme 8). The requisite γ-ketoacylpalladium derivatives can be generated by Pd-catalyzed carbonylation of either (*Z*)-ß-halo-α,ß-unsaturated ketones or an intramolecular or intermolecular combination of alkynes or alkenes and organic halides capable of undergoing oxidative addition with Pd, such as alkenyl, allyl, benzyl, and acyl halides. In the presence of a suitable base γ-ketoacylpalladium intermediates can be converted to the desired γ-alkylidenebutenolides and the corresponding butanolides (Scheme 9). The latter process in Scheme 9 involving formation of three C–C and one C–O bonds represents one of the most efficient routes to γ-alkylidenebutenolides, but it lacks the regioselectivity of the former. The results summarized in Table 5 indicate the potential generality and synthetic utility of this method, which should prove to be particularly useful in cases where the γ-alkylidene moiety is a part of a ring and may not be readily constructed by alkylidenation of preformed γ-lactones and their equivalents[66,67] (Scheme 10). The synthesis of **17** provides an efficient route to a promising antiulcer agent U-68,215 (**18**).[67]

Scheme 9



Scheme 10

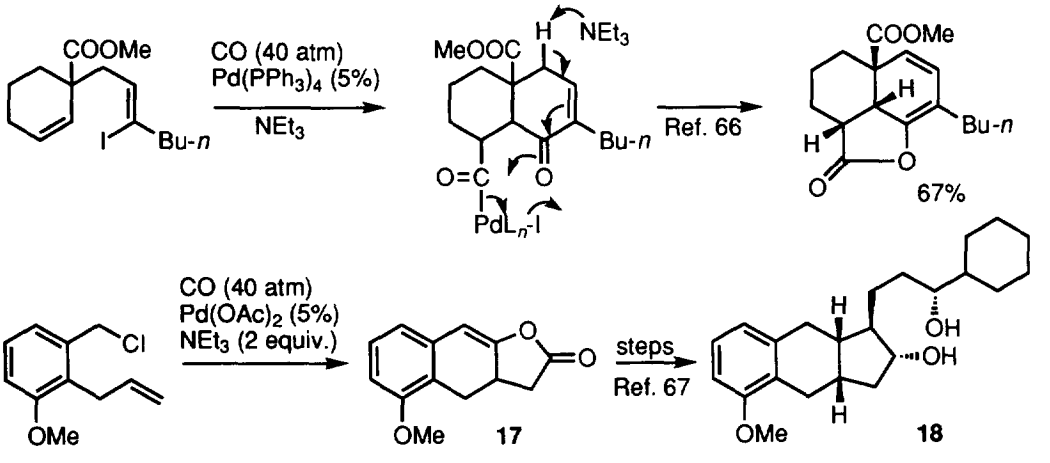
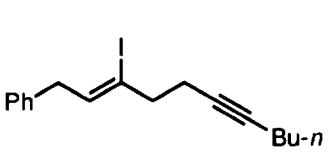
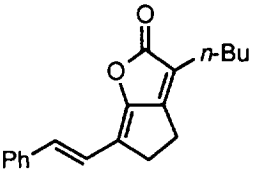
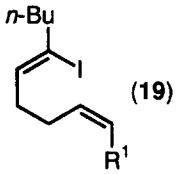
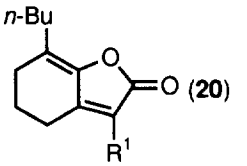
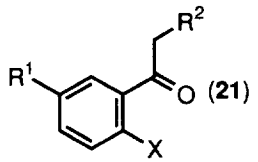
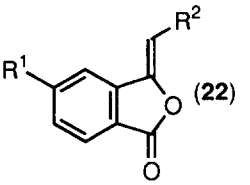
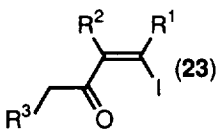
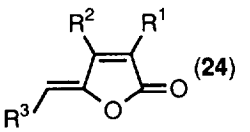


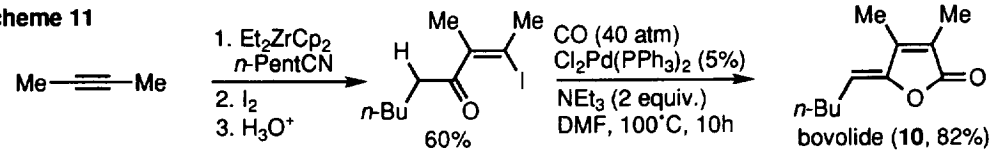
Table 5. Synthesis of γ-Alkylidenebutenolides via Pd-Catalyzed Carbonylation of Alkenyl and Aryl Halides or Triflates.

Substrate	Conditions	Product	Yield (%)	*Z/E*	Ref.
	**A**		73	—	68
 **(19)**		 **(20)**			
R^1 = H **(19a)**	**B**	**20a**	53	—	69
R^1 = Me **(19b)**	**B**	**20b**	24	—	69
 **(21)**		 **(22)**			
R^1 = H R^2 = Ph X = Br **(21a)**	**C**	**22a**	88	Z only	70
R^1 = OMe R^2 = Me X = OTf **(21b)**	**D**	**22b**	92	Z only	71
R^1 = H R^2 = *n*-Pr X = OTf **(21c)**	**D**	**22c**	86	Z only	71
R^1 = H R^2 = Ph X = OTf **(21d)**	**E**	**22d**	82	Z only	71
 **(23)**		 **(24)**			
R^1 = *n*-Pr R^2 = *n*-Pr R^3 = *n*-Pent **(23a)**	**A**	**24a**	75	Z only	27
R^1 = Ph R^2 = *n*-Pr R^3 = Me **(23b)**	**A**	**24b**	72	Z only	27
R^1 = Me R^2 = Me R^3 = *n*-Hept **(23c)**	**A**	**24c**	84	Z only	27
R^1 = *n*-Bu R^2 = H R^3 = Et **(23d)**	**A**	**24d**	80	81/19	27
R^1 = $PhCH_2$ R^2 = H R^3 = Me **(23e)**	**A**	**24e**	75	75/25	27

A: CO, $Cl_2Pd(PPh_3)_2$, NEt_3, DMF. **B**: CO, $Cl_2Pd(PPh_3)_2$, NEt_3, benzene. **C**: CO, $Pd(PPh_3)_4$, K_2CO_3, toluene. **D**: CO, $Pd(OAc)_2$, dppp, NEt_3, DMF. **E**: CO, $Pd(OAc)_2$, dppp, K_2CO_3, toluene.

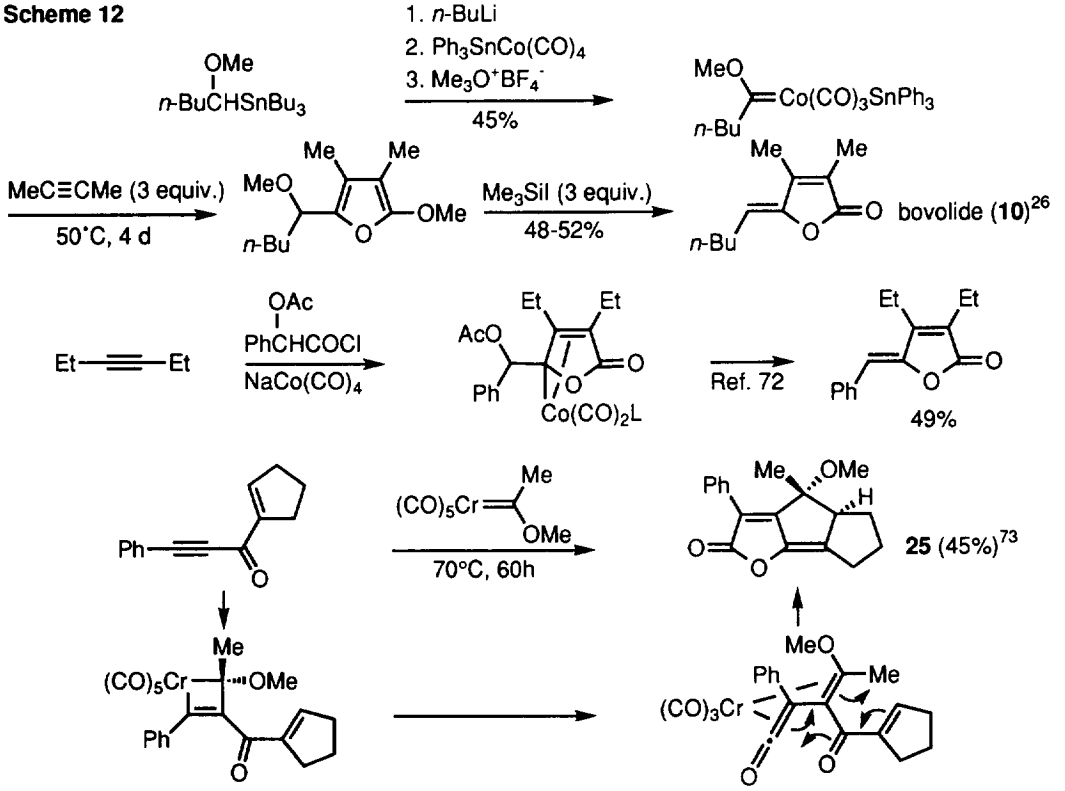
Although the Pd-catalyzed carbonylative method is intrinsically nonstereoselective, it generally provides ß-substituted (*Z*)-γ-alkylidenebutenolides in ≥98% stereoselectivity, which decreases to the 75 to 80% range in most cases where there is no ß substituent (Table 5). In general, however, the level of *Z* stereoselectivity appears to be considerably higher than most of the γ-alkylidenation reactions discussed earlier. A two-step synthesis of bovolide (**10**) from 2-butyne, hexanenitrile, and CO in ca. 50% overall yield and ≥98% stereoselectivity[27] indicates the potential synthetic utility of this method (Scheme 11).

Scheme 11



Other transition metals, such as Co[26,72] and Cr,[73] have been used in the synthesis of γ-alkylidenebutenolides via carbonylation of alkynes (Scheme 12). Although interesting and promising, these reactions as reported appear to be only stoichiometric in transition metals, limiting their synthetic utility. In the synthesis of **25**, the carbene-Cr complex presumably undergoes cyclic carbometallation to produce a metallacyclobutene which is converted via carbonylation to the ene-ketene-metal complex and then to γ-alkylidenebutenolides, as shown in Scheme 12.

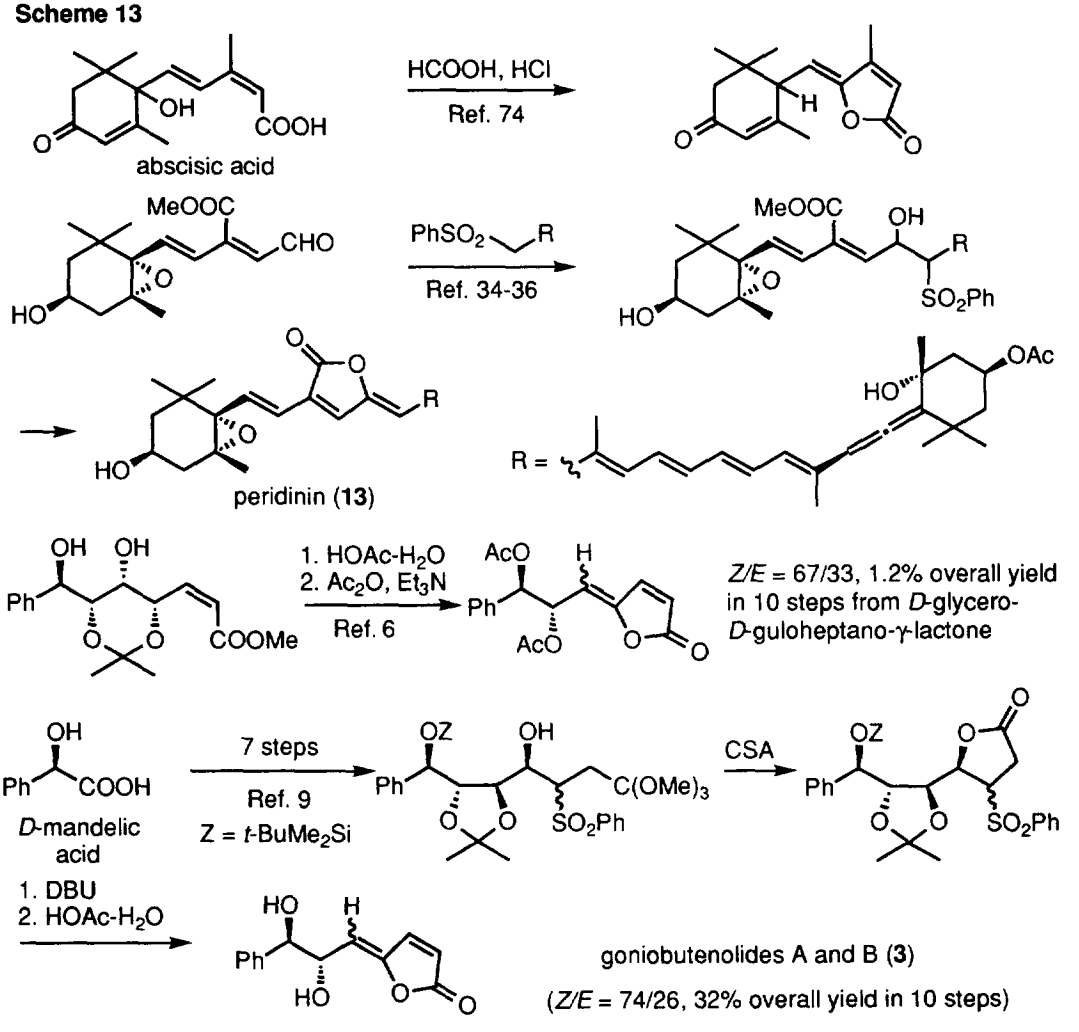
Scheme 12



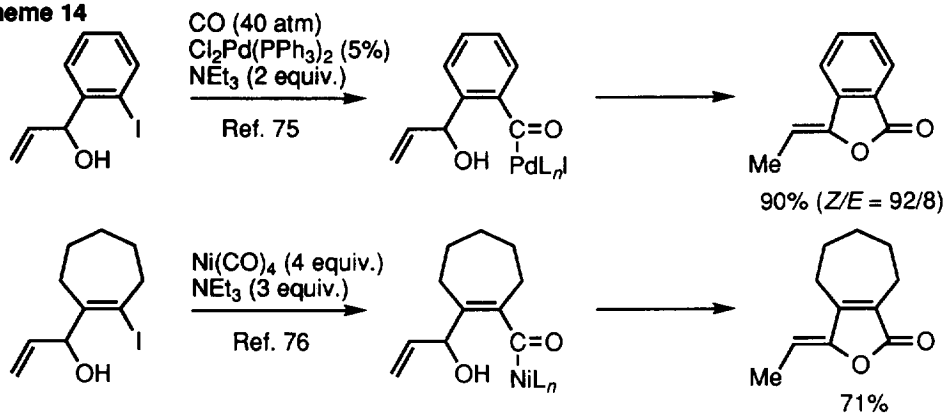
2. Via γ-Hydroxyacids

γ-Hydroxyacids are known to readily cyclize to give γ-lactones. In cases where such γ-lactones contain a suitable functional group, such as an allyl, alkenyl, halogen, oxygen, or sulfur group that can participate in elimination reactions, γ-alkylidenebutenolides and -butanolides can be obtained. Here again, the method is intrinsically nonstereoselective, but favorable results have been obtained in many cases presumably due to the higher thermodynamic stability of the desired isomer, *i.e.*, *Z* isomer in most cases. Some representative examples are shown in Scheme 13, and some related carbonylation reactions are shown in Scheme 14.

Scheme 13



Scheme 14

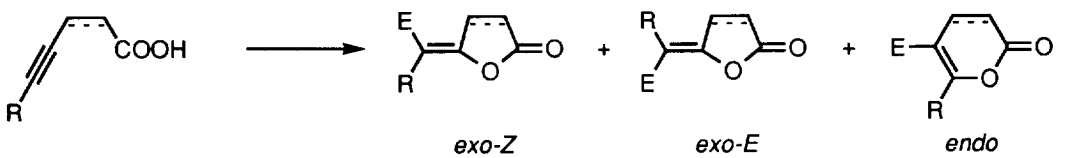


HIGHLY STEREOSELECTIVE SYNTHESES VIA 4-ALKYNOIC AND 4-ALKENOIC ACIDS

1. Via 4-Alkynoic Acids

In contrast with the intrinsically nonstereoselective methods discussed in the preceding sections, the lactonization reactions of 4-alkynoic acids can be essentially 100% stereoselective irrespective of substituents. Although basic conditions have been employed to effect lactonization in some cases, most of the cyclization agents are Lewis acidic. These reagents may be divided into non-metallic reagents, such as proton acids, and metallic reagents containing mostly heavy metals, such as Hg, Ag, Pd, and Rh. In addition to these reagents, *N*-halosuccinimides (NXS) containing I, Br, and Cl, in conjunction with some bases, such as $KHCO_3$ and Bu_4NOH, have been used to effect halolactonization. Although the relative merits and demerits of these competitive methods are not very clear, those involving transition metals, especially Ag and Pd, appear to be generally cleaner, more selective, and higher yielding. The Pd-catalyzed methodolgy is particularly promising and attractive in that (a) either *Z* or *E* isomers can be selectively obtained and (b) cross-coupling lactonization tandem process can provide a very efficient and satisfactory route to γ-alkylidenebutenolides. Various methods mentioned above are discussed below in some detail. In general, lactonization of 4-alkynoic acids involves stereoselective *trans* addition reactions producing γ-alkylidenebutenolides and -butanolides. In addition to the formation of unwanted stereoisomers, one of the major potential side reactions is the formation of six-membered lactones via *endo*-mode lactonization (Scheme 15).

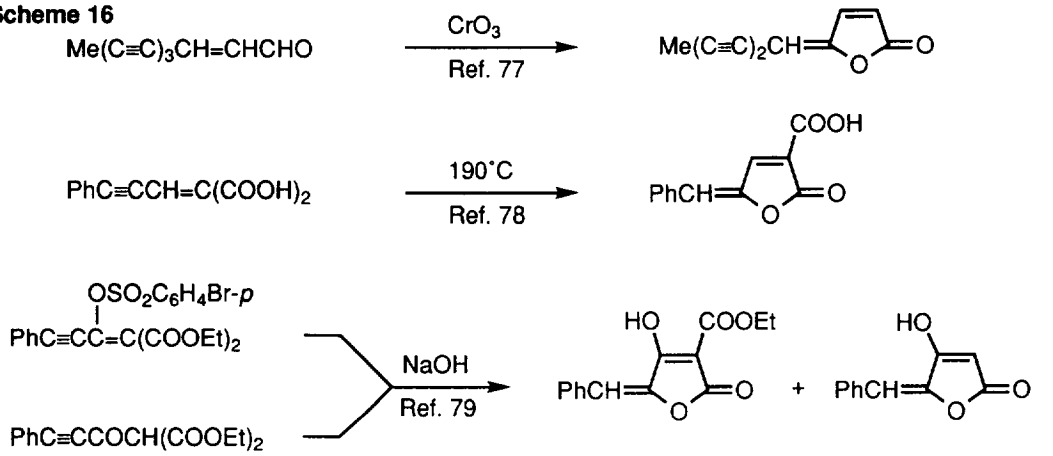
Scheme 15



a. Proton acid-catalyzed lactonization of 4-alkynoic acids

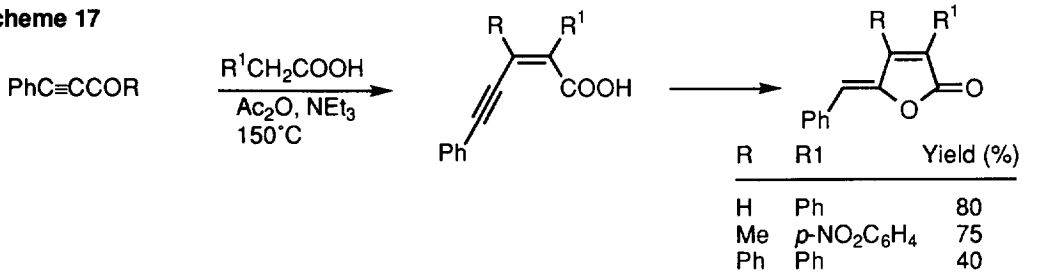
Some of the early syntheses of γ-alkylidenebutenolides were accidentally observed in attempts to prepare the corresponding alkynoic acids. In the examples shown in Scheme 16, the stereochemistry of the products was unspecified, although the *Z* geometry was mechanistically implicated in some cases.

Scheme 16



In later studies summarized in Scheme 17, however, the *Z* geometry of the products was claimed.[80] This simple method has not been widely used in recent years presumably because faster and possibly more favorable metal-catalyzed methods have been developed. Thus, its scope and limitations remain relatively ill-defined, even though it is clearly satisfactory in some cases.

Scheme 17



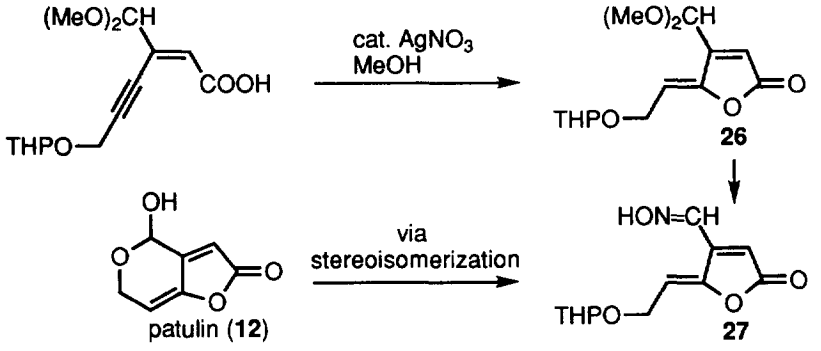
R	R1	Yield (%)
H	Ph	80
Me	*p*-$NO_2C_6H_4$	75
Ph	Ph	40

b. Ag- and Hg-catalyzed lactonization of 4-alkynoic acids

A remarkable rate acceleration in the lactonization of PhC≡CCH=C(COOH)$_2$ by $AgNO_3$ was observed as early as 1958.[78] In sharp contrast with the thermal cyclization process which required heating at 190 °C for 10-15 min, the same transformation in the presence of $AgNO_3$ (2.3 equiv) in EtOH–H_2O smoothly proceeded at room temperature to provide the same γ-alkylidenebutenolide in comparable yield (88%). The catalytic nature of the reaction was indicated in the synthesis of **26**, and its *Z* geometry was established by its conversion into patulin

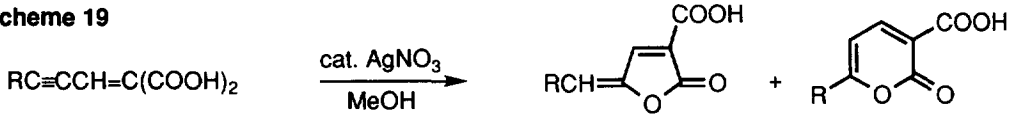
oxime **27** obtained from patulin, which was known to have the *Z* geometry[81,82] (Scheme 18). In general, the stereoselectivity of the Ag-catalyzed lactonization reaction appears to be high. However, an essentially 1:1 mixture of the *E* and *Z* isomers was obtained, albeit in high combined yield, by Ag_2CO_3-catalyzed lactonization of 4-nonynoic acid.[83]

Scheme 18



One major drawback of the Ag-catalyzed lactonization reaction is competitive formation of the corresponding α-pyrone as shown in Scheme 19.[84]

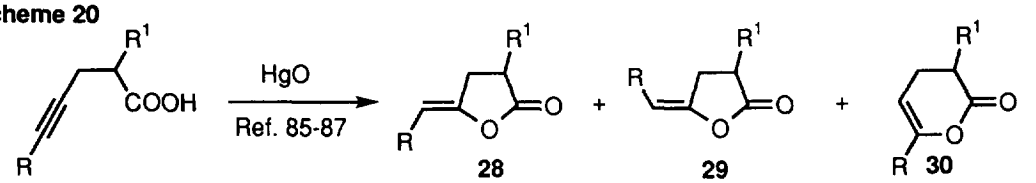
Scheme 19

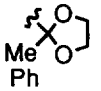


R = *n*-Bu (54/46)
R = Me (ratio unspecified)

Similarly, 4-alkynoic acids have been lactonized in the presence of catalytic amounts of Hg compounds, such as HgO, $Hg(OAc)_2$, and $Hg(OOCCF_3)_2$. Some early results are summarized in Scheme 20. Terminal alkynes appear to lactonize readily, whereas internal alkynes are more reluctant to lactonize. The latter alkynes also are prone to pyrone formation and stereoisomerization.

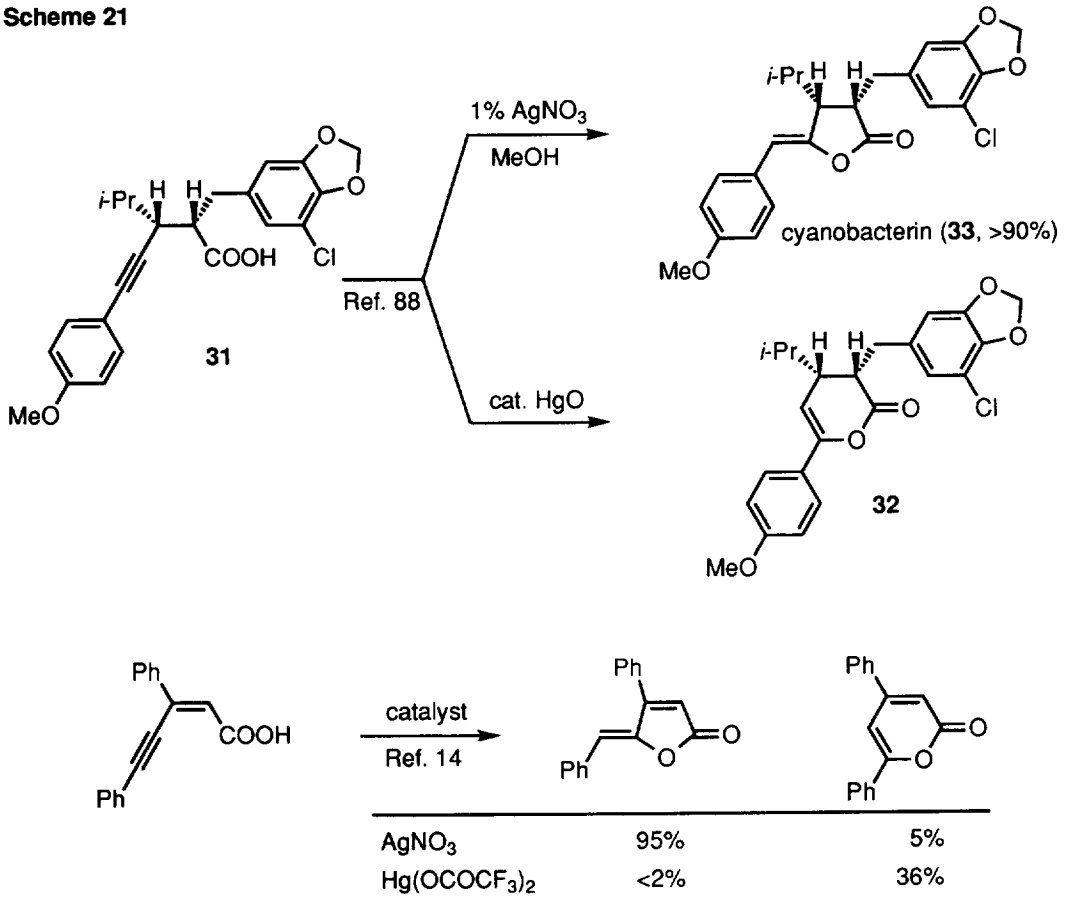
Scheme 20



R	R^1	Solvent	Temp. (°C)	Time (h)	Yield (%) 28	29	30
H	H	none	60	0.5	~100	—	—
H		none	60	0.5	98	—	—
H	Ph	$CHCl_3$	60	4	98	—	—
Ph	H	none	110	3	37	41 (**29+30**)	
Ph	H	DMF	reflux	2	83	9 (**29+30**)	
Ph	$PhC{\equiv}CCH_2$	DMF	reflux	2	76	7 (**29+30**)	

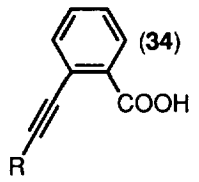
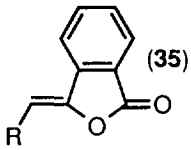
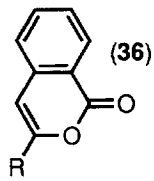
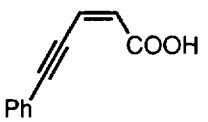
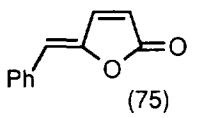
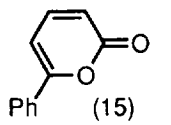
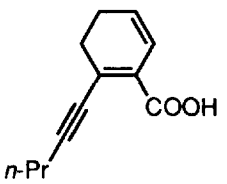
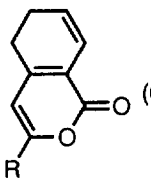
Although the results presented above do not readily permit comparison of the Ag- and Hg-catalyzed methods, there have been indications that, in some seemingly difficult cases, the Hg-catalyzed method fails to produce the desired γ-alkylidenebutenolides, while the Ag-catalyzed lactonization is satisfactory. Thus, for example, treatment of **31** with mercury(II) salts gives nearly exclusively **32**, whereas its treatment with 0.1 N $AgNO_3$ in MeOH provides the desired cyanobacterin (**33**) in over 90% yield.[88] Similar observations have also been made recently[14] (Scheme 21).

Scheme 21



A recent detailed study of Ag-catalyzed lactonization of 4-alkynoic acids indicates that even this reaction can give either butenolides or α-pyrones as the predominant product and that the ratio of the two products is strongly dependent on substrate structure, Ag salts, and solvents. In general, the use of either AgI or Ag metal and DMF favors the formation of butenolides.[38,39] (Table 6). We have recently found that high dilution also favors their formation.[14]

Table 6. Synthesis of γ-Alkylidenebutenolides via Ag-Catalyzed Cyclization of 4-AlkynoicAcids.

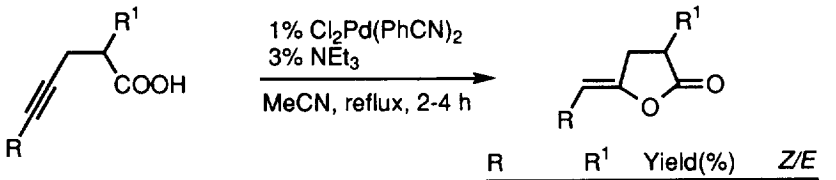
4-Alkynoic Acid	Catalyst[a]	Solvent	Product and yield (%) Butenolide[b]	Pyrone	Ref.
 (**34**)			 (**35**)	 (**36**)	85
n-Pr (**34a**)	Ag_2CO_3	dioxane	**35a** (14)	**36a** (71)	
n-Pr (**34a**)	Ag_2CO_3	benzene	**35a** (21)	**36a** (72)	
n-Pr (**34a**)	Ag_2CO_3	MeCN	**35a** (45)	**36a** (26)	
n-Pr (**34a**)	Ag_2CO_3	DMF	**35a** (75)	**36a** (15)	
n-Pr (**34a**)	$AgClO_4$	DMF	**35a** (2)	**36a** (93)	
n-Pr (**34a**)	Ag_2O	DMF	**35a** (39)	**36a** (58)	
n-Pr (**34a**)	AgI	DMF	**35a** (77)	**36a** (13)	
n-Pr (**34a**)	Ag	DMF	**35a** (82)	**36a** (13)	
t-Bu (**34b**)	Ag	DMF	**35b** (93)	**36b** (2)	
Ph (**34c**)	Ag	DMF	**35c** (100)	**36c** (0)	
	AgI	DMF	 (75)	 (15)	85
	Ag	DMF	**14**[c] (68)	 (6)	37

[a] 10 mol %. [b] *Z* only. [c] See Scheme 1.

c. Pd- or Rh-catalyzed lactonization of 4-alkynoic acids producing γ-alkylidenebutanolides

In addition to the Ag-catalyzed lactonization of 4-alkynoic acids, the Pd-catalyzed lactonization of 4-alkynoic acids, especially the Pd-catalyzed tandem cross coupling–lactonization protocol, has emerged as a highly efficient and selective method for the synthesis of γ-alkylidenebutenolides. However, its development has been evolutionary, and it may have originally stemmed from Schwartz' development of a Pd-catalyzed stereoselective cyclization of 4-alkynols.[90] However, it was Utimoto[91] who reported what appears to be the first set of examples of the Pd-catalyzed cyclization of 4-alkynoic acids to give γ-alkylidenebutanolides (Scheme 22). A combination of 1 mol% of $Cl_2Pd(PhCN)_2$ and NEt_3 (3 mol %) in MeCN was used as the reagent (Utimoto's conditions). Although the stereoselectivity for the synthesis of a (*Z*)-benzylidenebutenolide was reported to be 100%, that for alkylidene derivatives was ca. 85%.

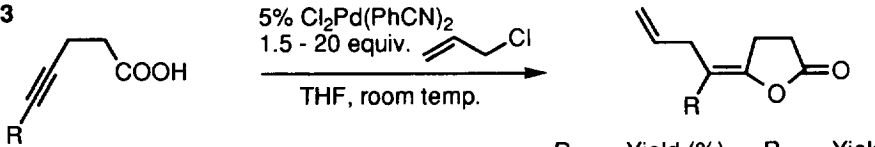
Scheme 22



R	R^1	Yield(%)	*Z/E*
Me	H	87	84/16
Ph	H	85	100/0
n-Hex	Ph	66	87/13

These workers also provided the first set of examples of the Pd-catalyzed tandem lactonization-cross coupling reaction using allyl and alkenyl halides as cross-coupling partners. A combination of 5 mol % of $Cl_2Pd(PhCN)_2$ and 1.5-20 equiv of an allyl or alkenyl halide in THF was used as the reagent. This tandem protocol provided a route to (*E*)-γ-alkylidenebutanolides. It has also been applied to the synthesis of a few butanolides containing a tetrasubstituted γ-alkylidene moiety[92] (Scheme 23). Although the level of stereoselectivity was not indicated, it was implicated to be high.

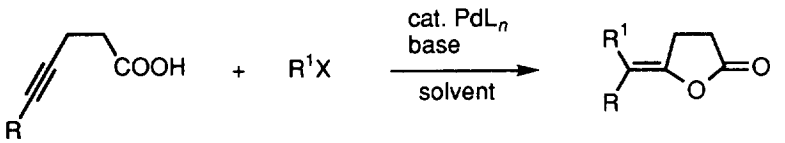
Scheme 23

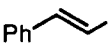
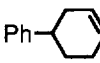


R	Yield (%)	R	Yield (%)
H	94	Ph	73
n-Hex	85	$SiMe_3$	76

Several other related procedures for the synthesis of (*E*)-alkylidenebutanolides patterned after Utimoto's tandem lactonization-cross coupling protocol have since been developed. The use of allyl 4-pentynoates requires just one equivalent of allyl group per 4-pentynoic acid.[93,94] The use of aryl and alkenyl halides and triflates,[95] alkynyl bromides,[96] and propargyl acetates[97] has also been reported (Scheme 24). An interesting extension of these studies is the development of an intramolecular tandem lactonization–cross coupling process reported[98] recently (Scheme 25). Another interesting variant involves trapping by conjugate addition in place of cross coupling[99] (Scheme 26). Some other noteworthy developments include lactonization reactions of 4-alkynoic acids catalyzed by a novel mixed metal sulfide cluster, $[PdMo_3S_4(1,4,7\text{-triazacyclononane})_3Cl](PF_6)_3$,[100] and $[ClRh(Cy_2PCH_2CH_2PCy_2)]_2$.[101,102] Although the superiority of the Rh catalyst relative to Pd catalysts, such as $Pd(PPh_3)_4$, was claimed, the currently available data on the Pd-catalyzed reaction suggest that the conditions used for this reaction by the authors were far from being optimized. Thus, the relative merits and demerits of Rh and Pd catalysts remain unclear, although Rh catalysts do appear to be promising. Throughout these studies, however, neither γ-alkylidenebutenolides nor γ-alkylidenebutanolides of natural origin were reported.

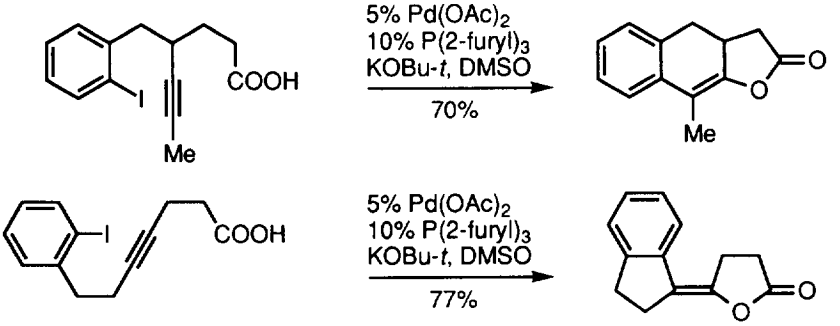
Scheme 24



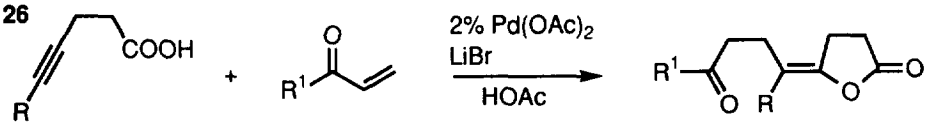
R	R^1X	Catalyst	Yield(%)	Ref.
H	PhI	$Pd(PPh_3)_n$, NEt_3, DMSO or THF	82	95
H		$Pd(PPh_3)_n$, NEt_3, DMSO or THF	74	95
p-$MeOC_6H_4$	PhI	$Pd(PPh_3)_n$, NEt_3, DMSO or THF	65	95
H		$Pd(PPh_3)_n$, NEt_3, DMSO or THF	74	95
H	*n*-BuC≡CBr	$Pd[P(2\text{-furyl})_3]_n$, KOBu-*t*, DMSO	84	96
H	$HC{\equiv}CCMe_2OAc$[a]	$Pd[P(2\text{-furyl})_3]_n$, KOBu-*t*, DMSO	61	97

[a] In the product, $R^1 = Me_2C{=}C{=}CH$-.

Scheme 25



Scheme 26

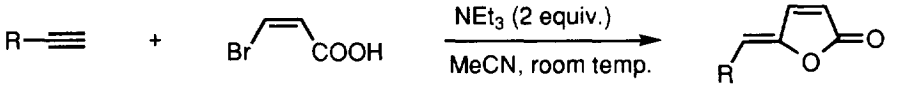


R	R^1	Yield (%)
H	H	66
Ph	H	85
H	Me	65

d. Pd-catalyzed efficient and stereoselective synthesis of γ-alkylidenebutenolides via tandem cross coupling-lactonization

During the course of an investigation of the trapping of γ-ketoacylpalladium derivatives with *in situ*-generated enolates, the authors became interested in developing highly efficient and selective procedures for the synthesis of a variety of γ-alkylidenebutenolides, especially the *Z* isomers, such as those shown in Scheme 1. Although the method summarized in Scheme 9 was satisfactory in some cases where the presence of a ß-substituent apparently forces the γ-alkylidene moiety to be *Z*, as in the synthesis of bovolide (Scheme 11), a significantly lower level of stereoselectivity (ca. 75-80% *Z*) appeared to be typical in cases where the ß position is unsubstituted. A more basic problem was the difficulty in synthesizing the required precursors in some cases. The authors' attention was then drawn to a tandem cross coupling-lactonization process converting terminal alkynes and (*Z*)-ß-haloacrylic acids into (*Z*)-γ-alkylidenebutenolides (91-97% *Z*) in moderate to good yields, which was reported to be a serendipitous discovery in an attempt to achieve Pd-catalyzed yne-ene cross coupling[104] (Scheme 27). A combination of 3% each of $Cl_2Pd(PPh_3)_2$, CuI, and NEt_3 (2 equiv) in MeCN was used for the reported transformation, and a two-cycle mechanism consisting of (i) Sonogashira-type cross coupling,[105] (ii) $HPdL_n$-induced *anti*-lactonization, and (iii) reductive elimination was suggested. A closely related reaction of *o*-iodobenzoic acid with alkynes was also reported independently.[106] The reagent system was very similar to that described above, but DMF and DMSO were mainly used as solvents.

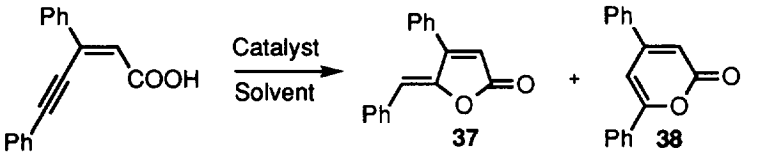
Scheme 27



R	Yield (%)	*Z*/*E*	R	Yield (%)	*Z*/*E*
Ph	80	>97/3	$THPOCH_2$	62	93/7
n-Pent	60	91/9	$Me_2C(OH)$	86	94/6
PhCH(OH)	56	>97/3			

While moderately satisfactory for the cases where unsubstituted (*Z*)-ß-bromoacrylic acid was used as a reagent, further development was clearly needed for other cases. As it was difficult to dissect various reaction parameters in the tandem process involving two discrete steps, (*Z*)-3,5-diphenyl-2-pent-4-ynoic acid was prepared by the Pd-catalyzed cross coupling reaction of PhC≡CZnBr with (*Z*)-3-iodo-3-phenylpropenoic acid, and its lactonization was studied using Pd, Ag, and Hg catalysts. The results are summarized in Table 7.[14]

Table 7. Lactonization of (Z)-2,5-Diphenyl-2-penten-4-ynoic Acid Catalyzed by Metal Complexes Containing Pd, Ag, and Hg



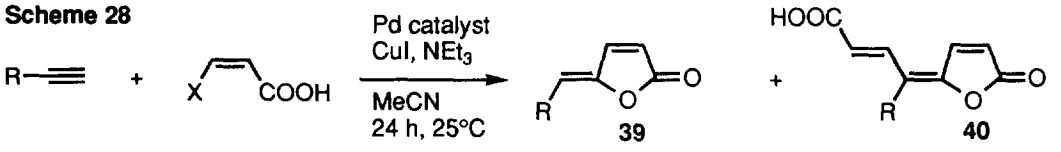
Catalyst	Solvent	Time[a](h)	Yield[b] (%) 37	38
$Pd(PPh_3)_4$	CH_3CN	24	83	6
$Pd(PPh_3)_4$	DMF	24	64	17
$Pd(PPh_3)_4$	THF	24	20	22
$PdCl_2(PPh_3)_2$	CH_3CN	24	27	10
$Pd(dba)_2 + 2PPh_3$	CH_3CN	24	27	6
$Pd(OAc)_2 + 2PPh_3$	CH_3CN	24	17	27
$PdCl_2(PhCN)_2$	THF	24	53	31
$PdCl_2(PhCN)_2$	CH_3CN	24	50	44
$AgNO_3$[c]	CH_3OH	1	95	5
$Hg(OCOCF_3)_2$	CH_2Cl_2	192	<2	36

[a] Unless otherwise mentioned, the reaction was run at 25°C. [b] ^1H NMR yield.
[c] The **37/38** ratio of 95/5 was observed at ≤0.01M in alkynoic acid.
At its concentration of 0.1M, the ratio was 74/26.

The results shown in Table 7 indicate the following. Phosphine-free catalysts, such as $Cl_2Pd(PhCN)_2$ used by Utimoto[91] for the synthesis of butanolides, or $Cl_2Pd(PPh_3)_2$ used by Lu[104] are at best moderately satisfactory, and a significant amount of 4,6-diphenyl-α-pyrone may be formed as a byproduct. In general, competitive formation of α-pyrones can be a serious side reaction, and the butenolide/α-pyrone ratio should be closely monitored. This may be one of the critical differences between the cases of γ-butanolides and those of γ-butenolides. Somewhat unexpectedly, the most satisfactory results have been obtained with $Pd(PPh_3)_4$ or its

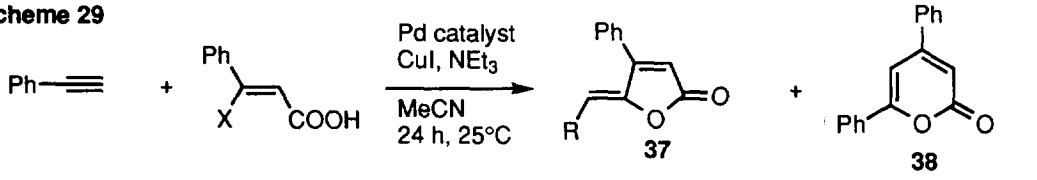
equivalents in which the P/Pd ratio is ≥4 in MeCN. The use of THF is relatively unsatisfactory. Whereas $Hg(OOCCF_3)_2$ is almost totally unsatisfactory, $AgNO_3$ is very satisfactory provided that the concentration of the enynoic acid is kept at or below 0.01 *M*. Thus, at its concentration of 0.1 *M*, the γ-butenolide/α-pyrone ratio is only 74/26. At 0.01 *M*, however, the *Z*/*E* ratio is ≥50. The distinct advantage of the use of $Pd(PPh_3)_n$ complexes, where $n \geq 4$, is also clearly seen in the cross coupling-lactonization tandem processes shown in Schemes 28 and 29.[14] In these cases the α-pyrone formation does not appear to occur to any significant extent. On the other hand, the formation of **40** can be a serious side reaction to be avoided in the reaction shown in Scheme 28. The use of ≥4 equivalents of PPh_3 per Pd in conjunction with (*Z*)-ß-bromoacrylic acid limits the formation of **40** to the 5-10% level.

Scheme 28



X	Pd catalyst	Yield (%) 39	40
I	$Cl_2Pd(PPh_3)_2$	24	38
Br	$Cl_2Pd(PPh_3)_2$	42	27
I	$Pd(PPh_3)_4$	46	23
Br	$Pd(PPh_3)_4$	74	11
Br	$Cl_2Pd(PPh_3)_2$+2PPh_3	86	5

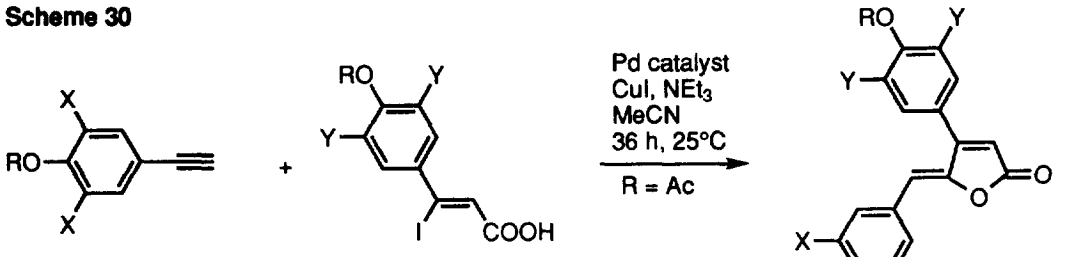
Scheme 29



X	Pd catalyst	Yield (%) 37	38
I	$Cl_2Pd(PPh_3)_2$	52	<2
Br	$Cl_2Pd(PPh_3)_2$	55	4
I	$Pd(PPh_3)_4$ or $Cl_2Pd(PPh_3)_2$+2PPh_3 or $Pd(dba)_2$+4PPh_3	78-80	≤4
Br	$Pd(PPh_3)_4$	95	4

Rubrolide A diacetate (**41**) has been synthesized in 70% as shown in Scheme 30. The yield observed with $Cl_2Pd(PPh_3)_2$ is only 38%. In this case, the use of the corresponding bromide has led to a much lower yield (20%).[14] So, some optimization processes may be needed for individual cases. Three other rubrolide diacetates, *i.e.*, C, D, and E, have been synthesized, only under unoptimized conditions in 38-54% yields.

Scheme 30



41 (>98% *Z*)

A (**41a**) X = Br Y = Br 70% with $Pd(PPh_3)_4$, 38% with $Cl_2Pd(PPh_3)_2$

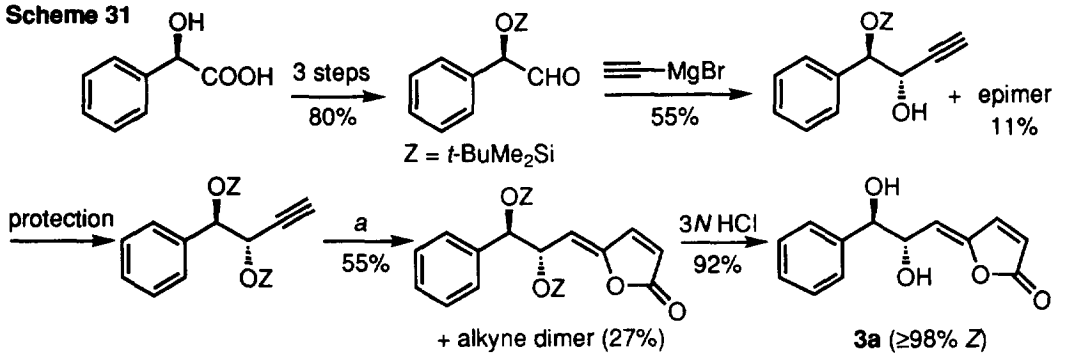
C (**41b**) X = Br Y = H 54% with $Cl_2Pd(PPh_3)_2$

D (**41c**) X = H Y = Br 54% with $Cl_2Pd(PPh_3)_2$

E (**41d**) X = H Y = H 50% with $Cl_2Pd(PPh_3)_2$

(+)-Goniobutenolide A (**3a**) was also synthesized in 6 steps in 21.4% overall yield from (*R*)-mandelic acid with essentially complete control of the exocyclic alkene geometry[10] (Scheme 31). In this case, however, dimerization of the starting alkyne was a serious side reaction, and the reaction conditions have not been optimized in this respect.

Scheme 31

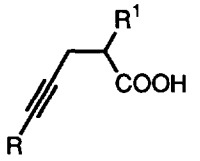


[a] (*Z*)-3-bromopropenoic acid, $Cl_2Pd(PPh_3)_2$ (5 mol %), $4PPh_3$, CuI (5 mol %), NEt_3, MeCN, 22°C, 48 h.

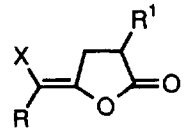
e. Halolactonization of 4-alkynoic acids

Treatment of 4-alkynoic acids with *N*-halosuccinimide (NXS) containing I, Br, or Cl, in the presence of $KHCO_3$ and Bu_4NOH in CH_2Cl_2–H_2O provides stereoselectively the corresponding *anti*-halolactonization products[87,103] (Scheme 32).

Scheme 32



NXS, $KHCO_3$
Bu_4NOH, CH_2Cl_2-H_2O
Ref. 87

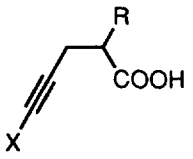


R	R^1	X	Yield(%)
H	Ph	I	81
Me	Ph	I	80
H	H	Br	70

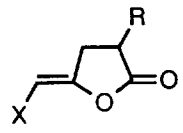
R	R^1	X	Yield(%)
H	Ph	Br	89
Me	Ph	Br	82
Me	Ph	Cl	82

It should also be noted that treatment of 5-halo-4-alkynoic acids with $Hg(OAc)_2$ or $Hg(OOCCF_3)_2$ provides stereoselectively the corresponding *syn*-halolactonization products[87,107] (Scheme 33). Either the *Z* or *E* isomers of iodoalkenes thus obtained can be used in the Pd-catalyzed cross-coupling reaction, as exemplified by the results shown in Scheme 34.[107]

Scheme 33



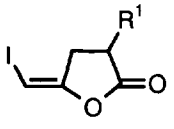
cat. Hg^{2+}



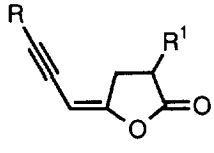
R	X	Hg^{2+} salt	Yield (%)	Ref.
H	Br	$Hg(OAc)_2$ or $Hg(OCOCF_3)_2$	60-62	83
H	Cl	$Hg(OAc)_2$ or $Hg(OCOCF_3)_2$	49-55	83

R	X	Hg^{2+} salt	Yield (%)	Ref.
H	I	$Hg(OCOCF_3)_2$	20	102
Bn	I	$Hg(OCOCF_3)_2$	—	102

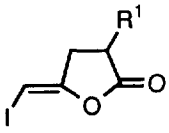
Scheme 34



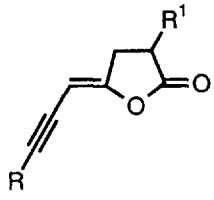
RC≡CH
cat. $Cl_2Pd(PPh_3)_2$
CuI, NEt_3



R = *n*-Hept, Ph, $SiMe_3$
R^1 = H, Bn, *i*-Pr, *n*-Bu



RC≡CH
cat. $Cl_2Pd(PPh_3)_2$
CuI, NEt_3

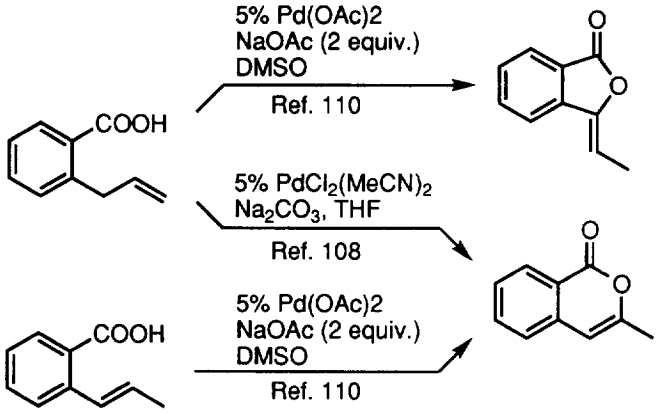


R = Me
R^1 = H, Bn

2. Via 4-alkenoic acids

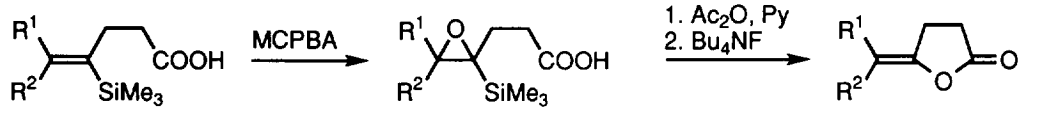
Lactonization of either *o*-alkenyl- or *o*-allylbenzoic acids tends to give isocoumarins rather than phthalides.[108,109] Under certain conditions, however, *o*-allylbenzoic acid selectively gives the corresponding phthalide, while *o*-(1-propenyl)benzoic acid gives the corresponding isocoumarins[110] (Scheme 35). The latter results can be readily explained in terms of *endo*-mode cyclization involving a benzylpalladium intermediate. More puzzling is the phthalide formation. The formation of a π-allylpalladium intermediate has been suggested. Although this particular transformation is highly selective, the reaction is not intrinsically stereoselective.

Scheme 35



A strictly stereospecific synthesis of γ-alkylidenebutanolides shown in Scheme 36 involves (i) generation of stereo- and regiodefined 4-silyl-4-alkenoic acids, (ii) their epoxidation, and (iii) desilylative ß elimination.[111] Although somewhat roundabout, it represents one of the relatively small number of highly stereoselective syntheses of γ-alkylidenebutanolides. However, it has not yet been applied to the synthesis of γ-alkylidenebutenolides.

Scheme 36



a: R^1 = *n*-Pent, R^2 = H. **b**: R^1 = H, R^2 = *n*-Pent. ≥99% stereoselective

CONCLUSION

Various options are available for the syntheses of γ-alkylidenebutenolides. Alkylidenation of oxygen-containing five-membered heterocycles is intrinsically nonstereoselective. This usually necessitates delicate stereoisomeric separation and limits the yield of the desired isomer. Particularly damaging is that the alkylidenation step generally occurs either in or near the final step. In cases where the formation of the undesired stereoisomer is strongly disfavored, as in the synthesis of nostoclides (Scheme 3), however, this synthetic strategy often offers simple and convenient routes to γ-alkylidenebutenolides. Another potentially useful finding is that the stereoselectivity level can be significantly modified and improved by separating the addition and elimination steps of alkylidenation. Thus, the usual *Z*/*E* stereoisomeric ratio of 1-4 can be improved to 10-20 through optimization of the elimination conditions (Scheme 5).

Most of the other methods except alkylidenation of 4-alkynoic acids are also intrinsically nonstereoselective, and the stereoselectivity is strongly substrate dependent. In general, the presence of a ß substituent in the betenolide ring moiety leads to a high *Z* selectivity, but its absence usually leads to a disappointingly low selectivity. However, some of these reactions can readily accommodate a γ-alkylidene unit incorporated in a ring which may not be readily accessible via alkylidenation of oxygen-containing five-membered heterocycles (Schemes 10 and 12).

Currently, highly stereoselective synthesis of γ-alkylidenebutenolides and -butanolides may be achieved in a predictable and satisfactory manner via simultaneous alkylidenation and lactonization of 4-alkynoic acids. The Ag-catalyzed method appears to be highly stereoselective, provided that competitive formation of α-pyrone can be suppressed, and the Rh-catalyzed method appears to be promising. By far the most extensively investigated and developed, however, is the Pd-catalyzed method. Various factors affecting the Pd-catalyzed reactions have been investigated. The optimal conditions may depend on the substrate structures. For the Pd-catalyzed cross coupling–lactonization (and γ-alkylidenation) tandem process producing γ-alkylidenebutenolides, the use of a Pd catalyst in conjunction with at least 4 equivalents of a phosphine, *e.g.*, PPh_3, in MeCN or some other polar solvent appears to be highly satisfactory. Either the *Z* or *E* isomer can be selectively produced through appropriate modifications.

Although further developments are desirable and undoubtedly forthcoming, it may now be stated that the synthetic organic chemists have at their disposal some highly stereoselective and efficient methods for the synthesis of γ-alkylidenebutenolides and related compounds which are applicable to the synthesis of not only those shown in Scheme 1 but also many others which will be isolated and identified in the future.

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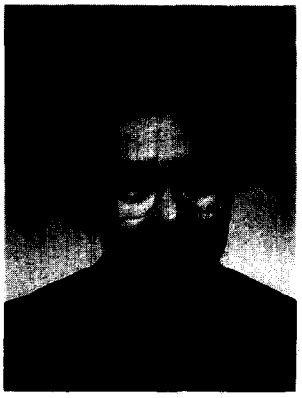
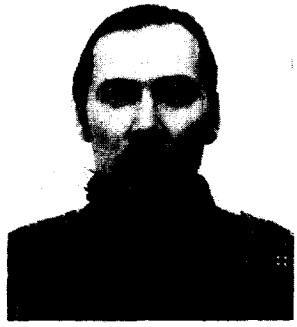
Biographical Sketch



Ei-ichi Negishi



Martin Kotora

Ei-ichi Negishi received the bachelor's degree from the University of Tokyo in 1958. While he was a research chemist at Teijin, Ltd., Japan, he came to the University of Pennsylvania as a Fulbright Scholar in 1960 and received his Ph.D. degree in 1963. He joined Professor H. C. Brown's research group at Purdue University as a postdoctoral associate in 1966 and became his assistant in 1968. In 1972 he moved to Syracuse University as Assistant Professor and was promoted to Associate Professor in 1976. He returned to Purdue University as Professor in 1979. He is the author of about 260 scientific publications. His recent work has centered on the use of transition-metal complexes as catalytic reagents in organic synthesis. Some transition metal-catalyzed reactions developed by him and his students include Pd- or Ni-catalyzed cross-coupling, Pd-catalyzed cyclic carbopalladation reactions, and Zr-or Ti-catalyzed carbometallation reactions.

Martin Kotora received his first degree from Charles University (Prague, Czech Republic) in 1986. He then moved to Institute of Chemical Process Fundamentals as a graduate student, and received a Ph.D. degree in 1991. After working in the same institute he joined Professor Takahashi's group at Institute for Molecular Science (Japan) as a JSPS Fellow in 1993. Two years later he joined Professor Negishi's group at Purdue University. His research interest lies in the development of new synthetic methodologies with emphasis on organometallic chemistry of both main group and transition metals and their application in organic synthesis.